Case-Based Learning in PHARMACOLOGY

for Undergraduate Medical Students

As per the latest CBME Guideline | Competency based
Undergraduate Curriculum for the Indian Medical Graduate

Snigdha Misra
Bhabagrahi Rath
Rajesh Kumar Suman

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to

my parents
Late Shri Sarat Kumar Senapaty
and
Smt Snehalata Senapaty

—**Snigdha Misra**

Foreword

Prescribing drugs is the most common healthcare intervention in our country. Understanding of the mechanism of action of drugs, their biochemical and physiological effects and their capacity for causing both beneficial and harmful clinical effects is essential and serves as a guide to good prescribing. Problem-based training in pharmacotherapy in undergraduate curriculum can significantly influence future prescribing. Also, pharmacology occurs at a critical juncture after the completion of basic science courses but before intense clinical experiences have begun. This book *Case-Based Learning in Pharmacology for Undergraduate Medical Students* has been designed to bridge the gap between theoretical knowledge and clinical practice. Case discussion on common clinical conditions takes into account students' knowledge, attitudes and skills and is targeted to promote more rational and safe use of medicine.

With the introduction of the latest CBME Guidelines | Competency Based Undergraduate Curriculum for the Indian Medical Graduate, case-based learning, an innovative teaching–learning tool, is gaining more importance. This book caters to the needs of the students and will enhance their critical thinking and analytical skills.

I congratulate the entire team (authors, contributors and CBS Publishers & Distributors) for bringing out this book on an important topic.

Dr Sudhir N Kadam

Medical Director and Trustee
MGM Medical College and Hospital
MGM Institute of Health Sciences
Kamothe, Navi Mumbai, Maharashtra

Preface

Undergraduate medical education has now become competency based, which means that it has become more practical, clinical application based and outcome-oriented. Hence, the teaching–learning methods have undergone a sea change from the conventional era.

This book *Case-Based Learning in Pharmacology for Undergraduate Medical Students* attempts to cater to the changing needs of the students in this CBME era. It is needless to say that the applied aspects of pharmacology could be appreciated by the students only with a proper understanding of the basic concepts. These two aspects are seamlessly integrated and presented in this book through the deliberately designed, still realistic case scenarios. Hopefully, the students of pharmacology, both undergraduate and postgraduate, as well as the teachers will like the 'Whys and Hows' format given in this book and find this resource useful.

We would want to hear, what you think, what you like about the book, and what you think could be improved? Please share your feedback by emailing to us at *cblinpharmac@gmail.com*

Snigdha Misra
Bhabagrahi Rath
Rajesh Kumar Suman

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I would like to express my deep and sincere gratitude to my teacher, Dr Jyotirmoyee Jena, who has been the Professor and Head, Department of Pharmacology, VSS Medical College, Odisha, during my undergraduate and postgraduate training, for guiding me both professionally and personally. Thank you for your support and keen interest in my academic achievements.

I would like to acknowledge Dr Sudarshan Pothal, from the Department of Pulmonary Medicine, VSS Medical College, Odisha, for his valuable inputs on the topic "Anti-tubercular Drugs".

This book would not have been possible without the contribution and support of Dr Sanjay Kumar, from Department of Pharmacology and Dr Divya Agarwal, Department of Anatomy of GSL Medical College, Rajahmundry, Andhra Pradesh.

I would like to thank my husband Mr Bhabani Shankar Misra and my brother Mr Satyajit Senapaty for continuous support and encouragement throughout this work. Special thanks to my lovely daughter, Miss Kashish Misra, for helping me in designing the flowcharts and schematic diagrams of this book.

Additionally, my sincere thanks to Mr SK Jain CMD and Mr YN Arjuna Senior Vice-President—Publishing, Editorial and Publicity (CBS Publishers & Distributors Pvt Ltd) for providing me an opportunity to author this book. Furthermore, the efforts put in by the editorial staff are highly commendable and appreciated.

Last but not least, I am very thankful to God for showering His blessings upon me.

Snigdha Misra

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Section I

Disorders of the Gastrointestinal System

1. Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

Chapter

1

Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

CASE 1: PEPTIC ULCER DISEASE (PUD)

A 35-year-old adult male RX, complains of intermittent pain in the upper abdomen. Pain aggravated at night after taking large meal. He was fond of fried and spicy food. He is a chronic smoker of cigarettes and an occasional drinker of alcohol. His grandmother had died of peptic ulcer disease. Haemoglobin values were normal and there was absence of blood in stool and vomiting.

The patient took ranitidine over the counter (OTC) for 3 times daily for a week for the relief of pain. Later after consultation with the physician ranitidine was changed to famotidine.

Qa. What are the factors which lead to peptic ulcer formation?

Imbalance between gastroduodenal mucosal defence forces and the aggressive forces lead to the pathogenesis of peptic ulcer. Thus, ***increase in acid-pepsin secretion and decrease in mucosal resistance*** appears to be the basic cause for peptic ulceration.

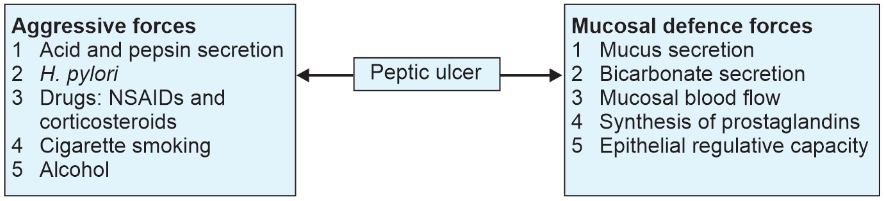
Aggressive forces
1 Acid and pepsin secretion
2 H. pylori
3 Drugs: NSAIDs and corticosteroids
4 Cigarette smoking
5 Alcohol
Peptic ulcer
Mucosal defence forces
1 Mucus secretion
2 Bicarbonate secretion
3 Mucosal blood flow
4 Synthesis of prostaglandins
5 Epithelial regulative capacity

Fig. 1.1: Interplay of factors that contribute to pathogenesis of peptic ulcer

Qb. Explain the regulatory mechanisms for acid secretion from gastric parietal cells.

Neurologic, physical and hormonal stimuli release acetylcholine, gastrin and histamine which bind to their respective receptors on the basement membrane of the parietal cell. Through a cascade of events, increased intracellular calcium and raised cyclic AMP activates protein kinase A which stimulates the proton pump, the final common pathway which transports H^+ out in exchange for K^+. Chloride ions transported into the stomach lumen associate with H^+ ions to form hydrochloric acid (HCl).

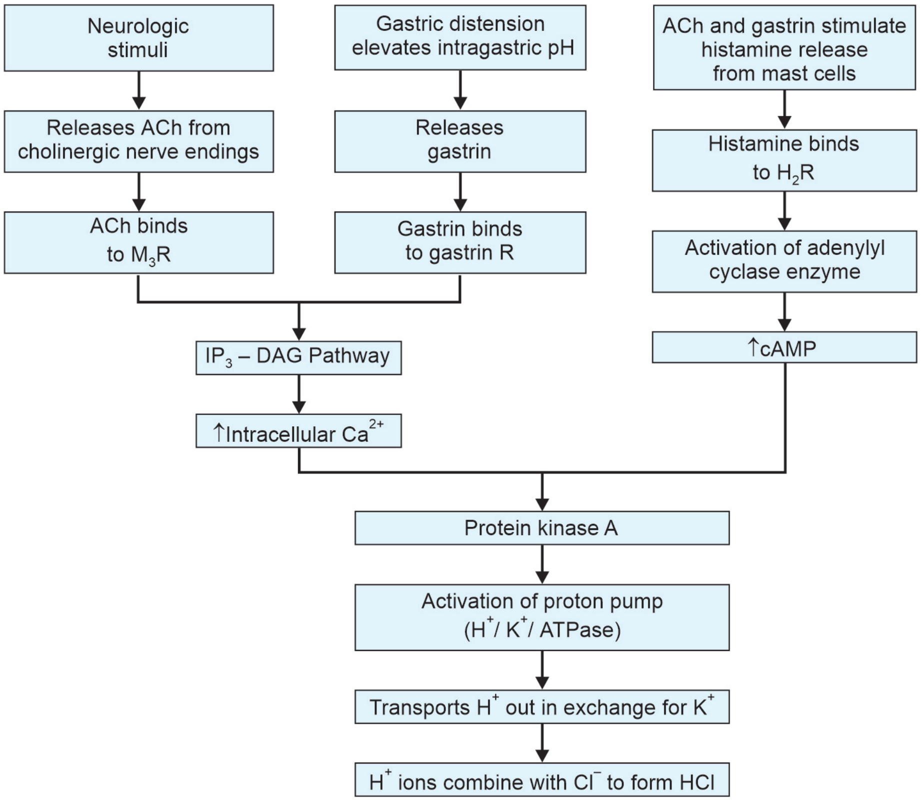
Neurologic stimuli
Releases ACh from cholinergic nerve endings
ACh binds to M_3R
Gastric distension elevates intragastric pH
Releases gastrin
Gastrin binds to gastrin R
ACh and gastrin stimulate histamine release from mast cells
Histamine binds to H_2R
Activation of adenylyl cyclase enzyme
↑cAMP
IP_3 – DAG Pathway
↑Intracellular Ca^{2+}
Protein kinase A
Activation of proton pump (H^+/ K^+/ ATPase)
Transports H^+ out in exchange for K^+
H^+ ions combine with Cl^- to form HCl

Fig. 1.2: Regulation of gastric acid secretion from the parietal cell

Qc. Which drugs are used for reducing acid secretion in peptic ulcer disease?

Drugs that reduce gastric acid secretion	
H2-receptor antagonists	Cimetidine, ranitidine, famotidine, nizatidine
Proton pump inhibitors	Omeprazole, rabeprazole, pantoprazole
Antimuscarinic agents	Pirenzepine, telenzepine
Prostaglandins	Misoprostol, enprostil, rioprostil

Qd. How is ranitidine or famotidine superior to cimetidine which is the prototypic H2- blocker in the treatment of dyspepsia?

Ranitidine and famotidine are superior to cimetidine in the following ways:

1. Both ranitidine and famotidine have greater potency and longer duration of action than cimetidine. This provides a longer duration of acid suppression.
2. Cimetidine crosses the blood–brain barrier and may induce mental confusion, headache and delirium. Ranitidine and famotidine have less penetration into the central nervous system, thereby producing less central adverse effects.
3. Cimetidine is antiandrogenic and increases prolactin levels, thereby leading to gynecomastia, galactorrhea, impotence and reduced sperm count in males. Hormonal side effects are minimal with ranitidine and famotidine.

4. Cimetidine inhibits CYP1A2, 2C9, 2D6 enzymes. Therefore, plasma levels of drugs metabolized by these enzymes may increase leading to toxicity. Ranitidine and famotidine have minimal or no action on hepatic CYP enzymes and decreased incidence of drug interactions.

Comparison of various H2-receptor antagonists

Parameters	*Cimetidine*	*Ranitidine*	*Famotidine*
Bioavailability	80	50	40
Relative potency	1	5–10	32
Half-life (hrs)	1.5–2.3	1.6–2.4	2.5–4
Duration of action (hrs)	6	8	12
Inhibition of CYP450	1	0.1	0
Dose mg (bd)	400	150	20

Qe. Mr RX, wishes to take a H2-antagonist before he takes alcohol to avoid gastric irritation. He consults you. Which H2-antagonist will you ask him to take?

Mr RX was recommended famotidine and nizatidine because these have minimal effect on hepatic cytochrome P450 enzymes and hence do not affect the metabolism of alcohol unlike other H2-blockers which act as inhibitors of cytochrome P450 and thus inhibit the gastric first pass metabolism of ethanol increasing the concentration of alcohol in the blood producing undesirable effects.

Case Continued

Mr RX experienced pain more frequently and periods of remission decreased. Endoscopic examination revealed active duodenal ulcer. Mucosal biopsy suggested *H. pylori*. A case of duodenal ulcer associated with *H. pylori* was confirmed.

Qa. Mention the treatment regimen you would recommend for *H. pylori* eradication in peptic ulcer disease in case of RX.

Proton pump inhibitor (PPI) based standard tripple therapy (PPI-clarithromycin-amoxicillin) is an acceptable first line management strategy for RX because he has not received clarithromycin previously and has no known allergy to penicillin. Amoxicillin is usually preferred initially because it is associated with a little or no bacterial resistance, has fewer adverse effects, and leaves metronidazole as an option for second-line therapies.

If RX had a documented allergy to penicillin, metronidazole can be used instead of amoxicillin in the PPI-based three-drug regimen.

Bismuth-based quadruple therapy containing a bismuth salt, metronidazole, tetracycline, and either a PPI or H2-receptor antagonist has been frequently used as second line therapy.

Qb. What is the reasonable treatment period of eradication therapy for *H. pylori* infections with treatment regimens?

A 10–14-day-regimen is superior to shorter treatment regimens and is less likely to be associated with antimicrobial resistance. A treatment duration of less than 7 days is not recommended and is associated with unacceptable eradication rates.

Qc. Mention the benefits of combination therapy for treatment of *H. pylori* infection associated peptic ulcer disease.

The following benefits are achieved with combination therapy for H. pylori eradication:

1. Combination therapy increases the effectiveness of antimicrobial treatment regimen with improved eradication rates and reduced relapse rate of *H. pylori* infections.
2. There is lower risk of development of drug resistance with combination therapy compared to single antibiotic regimen.
3. The addition of proton pump inhibitor raises the gastric pH which enhances the efficacy of antimicrobials leading to faster ulcer healing effect and reduced risk of relapse.

CASE 2: ANTACIDS IN THE TREATMENT OF PEPTIC ULCER DISEASE

Mr JK, a 35-year-old male, after dining with friends in restaurant felt abdominal discomfort, nausea and belching. The patient comes to your clinic at midnight complaining of heartburn and abdominal discomfort. You want to relieve his pain immediately.

Qa. Which drugs would you recommend that produce immediate effect?

The patient may be prescribed antacids because antacids neutralize the acid which has already been secreted in the stomach and produces immediate relief of symptoms. All other drugs act by inhibiting acid secretion and so may not relieve symptoms for at least 45 min.

Systemic and non-systemic antacids can be recommended for the treatment of dyspepsia which are as follows:

Drugs that neutralize acid secretion	
Systemic antacids	Sodium bicarbonate, Sodium citrate
Non-systemic antacids	Magnesium hydroxide, magnesium trisilicate, aluminium hydroxide gel, magaldrate, calcium carbonate

Case Continued

Mr JK was prescribed an antacid preparation containing aluminium hydroxide and magnesium hydroxide.

Qa. Is it rational to combine aluminium hydroxide and magnesium hydroxide in antacid preparations? Explain.

Aluminium containing antacids relax gastric smooth muscle and delay gastric emptying and cause constipation as a side effect. Magnesium hydroxide, on the other hand, causes osmotic diarrhea. The combination of aluminium hydroxide and magnesium hydroxide counterbalances the effects of each other and preserves the normal bowel function. Also, magnesium hydroxide is rapidly acting and aluminium hydroxide is slow acting so the combination provides a relatively fast and sustained neutralizing capacity.

Qb. Explain why sodium bicarbonate is not the preferred antacid in peptic ulcer disease.

Sodium bicarbonate is not the preferred antacid in peptic ulcer disease due to the following reasons:

i. Sodium bicarbonate forms HCO_3^- ion which reacts with hydrochloric acid (HCl) to form CO_2 as one of the products and this leads to distension of the stomach, belching and increases the risk of rupture or perforation of peptic ulcer.

ii. HCO_3^- ion if absorbed systemically causes metabolic alkalosis.
iii. Sodium absorption may lead to retention of water which may aggravate edema and symptoms of heart failure.
iv. There is risk of acid rebound as the duration of action is short lasting.

CASE 3: PROTON PUMP INHIBITORS FOR THE TREATMENT OF PEPTIC ULCER

VK, a 56-year-old male patient, was diagnosed with duodenal ulcer associated with NSAIDs, he was receiving for pain relief of rheumatoid arthritis.

He was prescribed enteric coated capsule of omeprazole 40 mg daily in the morning 30 minutes before breakast, for three weeks.

Qa. The half-life of proton pump inhibitors is 1.5 hours but these drugs are generally given once daily instead of more frequent administration. Justify with reasons.

Proton pump inhibitors (PPIs) are selective and irreversible inhibitors of H^+-K^+-ATPase transport system which is the final common pathway responsible for acid secretion. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane and this takes at least 18–20 hours. Therefore, acid suppression continues for about 20–24 hours despite the short half-life of proton pump inhibitor and elimination of the drug from the body.

PPIs are prodrugs which freely diffuse into the parietal cell compartment and after conversion into sulfenamide, an active metabolite, gets trapped within the parietal cell, forms one or more covalent disulphide bond with the sulfhydryl group of H^+-K^+-ATPase leading to longer duration of acid suppression.

Qb. Explain why omeprazole, a PPI, is given as enteric coated granules in capsules or enteric coated tablet in the treatment of peptic ulcer.

Proton pump inhibitors are acid labile and degraded in the acidic pH of the gastric juice in the lumen of the stomach. The enteric coating of omeprazole protects it from the damaging effect of acidic gastric juice, thereby facilitates the drug to reach the intestine, wherein presence of alkaline pH enteric coating dissolves releasing the drug in the intestine and improving the absorption and bioavailability of the drug.

CASE 4: MISOPROSTOL FOR THE TREATMENT OF PEPTIC ULCER

A 72-year-old female LM, presented with acute peptic ulcer like symptoms. She is a known case of rheumatoid arthritis and there is history of frequent intake of high dose of aspirin for pain relief.

Qa. Given that the patient's history is suggestive of intake of high doses of aspirin and older age as an independent risk factor for NSAID induced ulcer, what drugs would you recommend for the prevention of gastric ulcer?

Both misoprostol and proton pump inhibitors (PPIs) have a similar efficacy in preventing gastric ulcer, but proton pump inhibitors (PPIs) are better tolerated than prostaglandin analogs. Therefore, proton pump inhibitors are preferred for the treatment of NSAID-induced ulcer.

Qb. How does aspirin induce gastric mucosal damage and ulcer formation?

Aspirin is an acidic drug and is largely unionized at acidic gastric pH and is absorbed from the stomach. The unionized form of acidic drug crosses the membrane of gastric mucosal cell and is converted into the ionized form within the cell (pH 7.0). The ionized form of drug is trapped within the gastric mucosal cell causing injury to the mucosa and ulcer formation.

Aspirin like agents inhibit cyclooxygenase enzyme which mediates the formation of prostaglandins, that play a protective role on the gastric mucosa by enhancing the mucosal blood flow and reducing the gastric acid secretion. This reduces mucosal blood flow and produces areas of focal ischaemia and tissue damage which would subsequently be the sites of erosions and ulcers.

Qc. How is misoprostol useful in peptic ulcer disease?

Misoprostol, PgE1 analog has the following gastroprotective actions:

i. Increases mucus and bicarbonate secretion
ii. Enhances mucosal blood flow
iii. Increases in mucosal repair and restoration following gastric mucosal injury
iv. Inhibits gastric acid secretion in two ways: Directly by inhibiting acid secretion at the parietal cells and indirectly by inhibiting histamine release at enterochromaffin like cells.

CASE 5: MEDICATIONS FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) DURING PREGNANCY

A pregnant lady, Mrs TN visits the antenatal clinic with complains of heartburn and acid reflux and wishes treatment.

Qa. Which medications are safe and effective for heartburn during pregnancy?

H2-blockers or antacids may be used as first line agents for reflux. The use of proton pump inhibitors are reserved for more severe cases.

Ranitidine is the best studied agent effective for treatment of heartburn in pregnancy. Aluminium phosphate used as antacid therapy has been reported to provide complete relief of moderate to severe heartburn. Safety of proton pump inhibitors is not established in pregnancy. Misoprostol, a prostaglandin analogue, stimulates uterine contractions increasing the risk of abortion and early termination of pregnancy and therefore contraindicated in pregnancy.

Qb. Which drugs are preferred for the treatment of gastroesophageal reflux disease (GERD) in a non-pregnant adult?

In non-pregnant adults, proton pump inhibitors (PPIs) are more effective than antacids and H2-blockers for GERD and are preferred drugs.

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2. Franchi, C, Mannucci, P, Nobili, A, *et al*. Use and prescription appropriateness of drugs for peptic ulcer and gastrooesophageal reflux disease in hospitalized older people. *Eur J Clin Pharmacol* 76, 459–465 (2020). https://doi.org/10.1007/s00228-019-02815-w
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Section II

Disorders of the Respiratory System

2. Drugs for Bronchial Asthma

Chapter

2

Drugs for Bronchial Asthma

CASE 1: MODERATE PERSISTENT ASTHMA

RY, a 7-year-old girl, presents to the clinic with a history of asthma and seasonal allergic rhinitis (hay fever) each spring but not the rest of the year. She complains of shortness of breath and frequent night-time awakenings.

On enquiry, she revealed that her symptoms get worsened during spring season but over last 6 months she gives a history of three similar attacks which were of lesser intensity. The attacks were apparently spontaneous and occurred at an interval of around 1.5 to 2 months.

Medication history: **The attacks of bronchial asthma were well controlled previously with 2 puffs of salbutamol metered dose inhaler (MDI) taken as and when needed. However, the present attack did not subside in spite of 8 puffs of salbutamol MDI taken as 2 puffs every 10 minutes. She has been taking leukotriene receptor antagonist for allergic rhinitis.**

On examination: **Pulse is found to be 110/min and respiratory rate is 23/min. Examination of respiratory system reveals bilateral expiratory rhonchi with prolonged expiration. Rest of the systemic examination is normal.**

Past history: **Eczema and hay fever since she was 4 years old. There is no history suggestive of any cardiac cause of breathlessness or history suggestive of any abdominal or CNS problem.**

Your diagnosis: **Moderate persistent asthma.**

Qa. What could be the predisposing factor for bronchial asthma in case of RY?

Presence of allergic rhinitis and history of eczema and hay fever are important risk factors for asthma development. Patients with allergic rhinitis have threefold greater chance of developing asthma.

Qb. Describe the underlying pathophysiology of bronchial asthma that causes signs and symptoms as described in the case of RY.

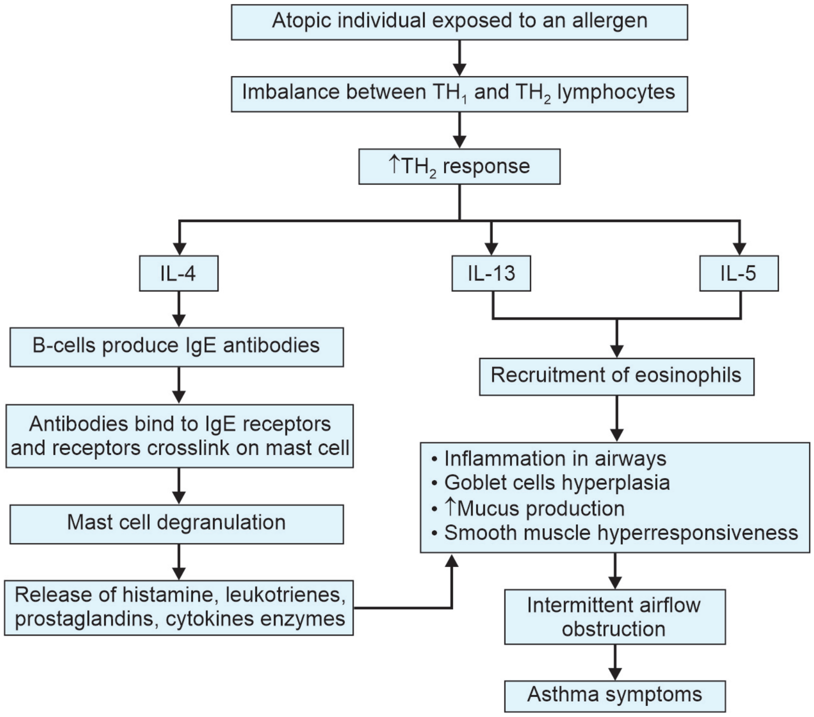

Atopic individual exposed to an allergen
Imbalance between TH1 and TH2 lymphocytes
↑TH2 response
IL-4
IL-13
IL-5
B-cells produce IgE antibodies
Antibodies bind to IgE receptors and receptors crosslink on mast cell
Mast cell degranulation
Release of histamine, leukotrienes, prostaglandins, cytokines enzymes
Recruitment of eosinophils
• Inflammation in airways
• Goblet cells hyperplasia
• ↑Mucus production
• Smooth muscle hyperresponsiveness
Intermittent airflow obstruction
Asthma symptoms

Fig. 2.1: Pathophysiology of asthma

Asthma is a disease of chronic airway inflammation in which allergen-specific T-helper-2 cells play a central role. There is increased production of T-helper-2-associated cytokines, such as interleukin (IL)-4, IL-13, and IL-5.

Interleukin-4 is a key cytokine in the development of allergic inflammation. It is associated with the secretion of IgE by B lymphocytes. Interleukin-4 also has the ability to upregulate IgE-receptors on the surface of mast cells. IgE-mediated activation of mast cell leads to degranulation and release of histamine and leukotrienes that promote cellular inflammation and lung remodelling in chronic asthma.

Interleukin-13 is implicated as a central regulator of eosinophilic inlammation, mucus hypersecretion, airway hyper-responsiveness and fibrosis.

Interleukin-5 is a powerful proinflammatory cytokine that is responsible for maturation, proliferation, activation and migration of eosinophils from bloodstream to the airways.

Qc. Which drugs are available for the management of bronchial asthma?

Bronchodilators

1. Selective β2-agonist: Salbutamol, terbutaline, salmeterol, formoterol
2. Non-selective sympathomimetics: Epinephrine, ephedrine, isoprenaline
3. Anticholinergics: Ipratropium bromide, tiotropium bromide
4. Methyxanthines: Theophylline, aminophylline

Corticosteroids

1. Oral: Prednisone, prednisolone and methylprednisolone
2. Parenteral: Methylprednisolone, hydrocortisone, sodium succinate
3. Inhalational: Beclomethasone, fluticasone, budesonide, flunisolide and ciclesonide

Mast Cell Stabilisers

Sodium chromoglycate and nedocromil sodium

Leukotriene Modulators

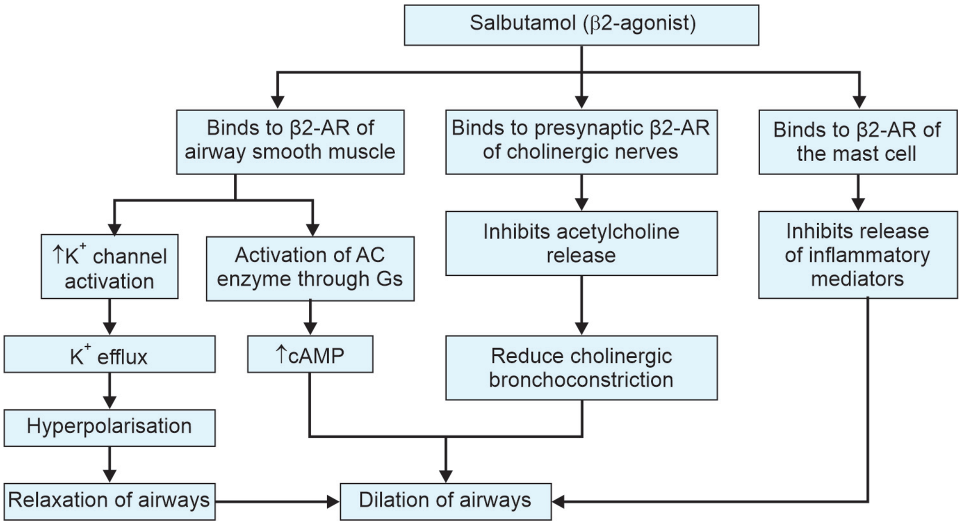
1. 5-Lipoxygenase inhibitor: Zileuton
2. Leukotriene receptor antagonists: Zafirlukast, montelukast, pranlukast

Biologicals

Monoclonal anti-IgE antibody: Omalizumab

Interleukin-5 (IL-5) pathway inhibitors: Mepolizumab, benralizumab

Qd. How does salbutamol relieve symptoms of asthma?


Salbutamol (β2-agonist)
Binds to β2-AR of airway smooth muscle
Binds to presynaptic β2-AR of cholinergic nerves
Binds to β2-AR of the mast cell
↑K$^+$ channel activation
Activation of AC enzyme through Gs
Inhibits acetylcholine release
Inhibits release of inflammatory mediators
K$^+$ efflux
↑cAMP
Reduce cholinergic bronchoconstriction
Hyperpolarisation
Relaxation of airways
Dilation of airways

AR: Adrenergic receptor, AC: Adenylyl cyclase, Gs: Stimulatory G protein

Fig. 2.2: Mechanism of action of salbutamol

Salbutamol acts as a bronchodilator due to its stimulatory effect on β2-adrenergic receptors at various sites:

1. Stimulation of β2-adrenergic receptors in the airway smooth muscle activates adenylyl cyclase (AC) and causes cyclic AMP mediated relaxation of airways. β2-agonists open large conductance calcium activated potassium channels causing potassium efflux and hyperpolarization of airway smooth muscle cells. Decreased intracellular calcium concentration together with increased membrane potassium conductance leads to smooth muscle relaxation and bronchodilation.
2. Stimulation of β2-adrenergic receptors at the presynaptic cholinergic nerve endings has an inhibitory effect on the release of acetylcholine and reduced cholinergic bronchoconstriction.

3. Stimulation of β2-adrenergic receptors on the mast cells inhibit the release of inflammatory mediators such as histamine and leukotrienes which are potent bronchoconstrictors.

Qe. Why is salbutamol preferred over isoproterenol and adrenaline in the management of acute symptoms of asthma?

Isoproterenol is a β1- and β2-adrenergic receptor agonist. Although it causes β2-mediated relaxation of the airways, the β1-stimulatory action on the heart increases the risk for tachycardia and arrhythmias.

Adrenaline is a non-selective adrenergic agonist that stimulates α, β1- and β2-receptors. Acting via α-receptors it causes peripheral vasoconstriction leading to rise in blood pressure and through β1-agonistic action causes cardiac effects like tachycardia and arrhythmias.

Salbutamol unlike adrenaline and isoproterenol, has selective β2-agonistic action. There is relaxation of airway smooth muscle reducing airflow obstruction and this provides relief of acute symptoms of asthma. Therefore, the beneficial effects of salbutamol can be achieved while cardiac side effects can be avoided.

Qf. What are the likely side effects of salbutamol use in bronchial asthma?

The side effects of salbutamol are more prominent with systemic administration and at higher dosages. They are the following:

1. Tremor or shakiness may be attributed to the stimulation of β2-receptor of the skeletal muscle.
2. Palpitation may be experienced by the patient due to β2-mediated vasodilation-induced reflex tachycardia. Cardiac effects are more common with non-specific agonists due to their additional β1-stimulatory action on heart.
3. Decrease in potassium concentration may occur due to β2-adrenergic activation of the Na^+-K^+-pump leading to transport of potassium intracellularly. A β2-adrenergic-mediated increase in glucose and insulin secretion also can contribute to the intracellular shift of potassium causing hypokalemia.

Qg. Aerosolized salbutamol is preferred over oral or parenteral administration in the management of acute asthma. Why?

It has been documented that inhaled route of salbutamol administration exerts as great or greater beneficial effect on pulmonary function tests with fewer systemic side effects than either the parenteral or oral routes. It has a rapid onset of action (15–30 min), a peak effect at 30–60 min and duration of action of approximately 4 to 6 hours. This time course of drug action makes salbutamol a suitable drug for quick relief of acute symptoms of asthma and is therefore frequently used as rescue treatment for all asthma patients. Salbutamol should not be administered orally to treat acute episode of severe asthma because of slow onset of action, lower efficacy and erratic absorption.

Qh. What could be the reason for lack of response to therapy with multiple doses of salbutamol in patient RY? What are the drawbacks of using salbutamol frequently, as monotherapy on long-term basis to control asthma?

Salbutamol has a short duration of action which is inadequate for control of nocturnal symptoms. Lack of response to therapy with multiple doses of salbutamol may be attributed to severity of airway obstruction with inflammation playing an important part in progression of asthma attack. Receptor subsensitivity to salbutamol, administered in repeated doses on a long-term basis could be a reason for reduction in duration of response with a little or no effect on intensity of response.

Long term and repeated use of salbutamol without controller and prophylaxis medication can increase asthma related complications with increased severity of asthma exacerbations, cardiac arrhythmias and hypertension. With frequent usage over a long period, it becomes ineffective and may lead to hyperinflation of lungs. It may mask the patient's perception of deteriorating lung function and increase morbidity in patients.

Qi. What change in treatment strategy should you consider in management of bronchial asthma, in case of RY?

Bronchial asthma in case of RY, which was previously intermittent in nature converts to moderate persistent asthma with worsening of symptoms of allergic rhinitis. This is because airway inflammation is an important component in the pathogenesis of asthma. So there is a need for therapy to reduce airway inflammation. Therefore, inhaled corticosteroids should be introduced which not only offers excellent relief of nasal symptoms but also improves asthma control.

According to 2021 GINA Report, Global Strategy for Asthma Management and Prevention, a reasonable treatment option for RY. is the following:

Preferred reliever medication	Low-dose inhaled corticosteroid (ICS)-formoterol as needed
Preferred controller medication	Daily low-dose inhaled corticosteroid (ICS) combined with a long-acting inhaled β2-agonist (LABA).

Case Continued

Treatment in RY was switched to a daily dose of combination inhaled steroid and long-acting beta-agonist (fluticasone propionate 150 μg and 5 μg formoterol twice daily). As a reliever medication low-dose inhaled corticosteroid (ICS)-formoterol was used.

Qa. Explain the rationale for combining inhaled corticosteroid (ICS) with formoterol, a long-acting beta-adrenergic agonist (LABA) in the management of moderate persistent asthma as in case of RY.

The primary aim of therapy in mild to moderate persistent asthma is to reduce disease exacerbation and improve asthma control. Formoterol is long-acting beta-agonist (LABA) which has a 12 to 24 hours duration of action. This profile makes long-acting inhaled β2-agonist a good option for control of nocturnal asthma and for prevention of bronchoconstriction or prophylaxis.

β2-agonists and corticosteroids act synergistically through different mechanisms to produce beneficial effects. β2-agonists act directly on airway smooth muscle and cause bronchodilation while steroids suppress inflammation which would impede relaxation of the smooth muscle.

Steroids increase β-adrenergic responsiveness which would otherwise decrease on long term and repeated use of beta-adrenergic agonists. β2-adrenoceptors are transcriptionally upregulated causing partial reversal of the degree of loss of surface receptors that occur during homologous desensitization to sustained agonist stimulation.

Qb. Which are the molecular mechanisms through which inhaled corticosteroids (ICS) suppress inflammation in asthma?

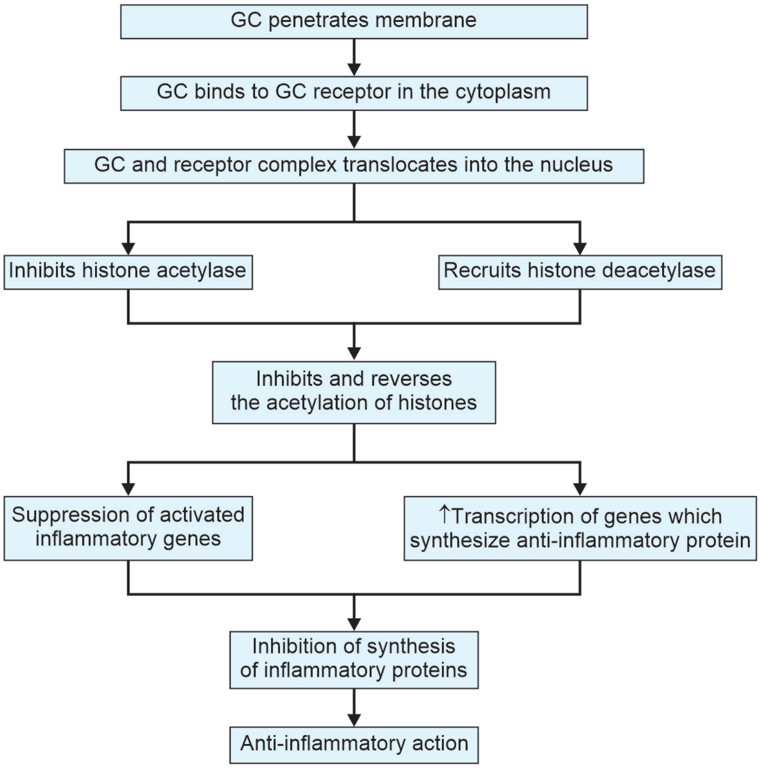

GC penetrates membrane
GC binds to GC receptor in the cytoplasm
GC and receptor complex translocates into the nucleus
Inhibits histone acetylase
Recruits histone deacetylase
Inhibits and reverses the acetylation of histones
Suppression of activated inflammatory genes
↑Transcription of genes which synthesize anti-inflammatory protein
Inhibition of synthesis of inflammatory proteins
Anti-inflammatory action

Fig. 2.3: Regulatory actions of glucocorticoids (GCs) on inflammatory cells

Inhaled glucocorticoids suppress inflammation mainly by switching off multiple activated inflammatory genes through reversing histone acetylation via recruitment of histone deacetylase 2 (HDAC2). The mechanisms which may contribute to the anti-inflammatory actions of corticosteroids include:

- Decreased transcription of genes in airway epithelial cells coding for pro-inflammatory proteins IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, IL-13, IL-15, TNF and GMCSF.
- Increased transcription of genes coding for anti-inflammatory proteins such as IL-10, IL-12 and IL-1R antagonist.

Qc. What are the clinical benefits of inhaled corticosteroids in bronchial asthma patients?

- Inhaled corticosteroids (ICS) are effective in *controlling asthma symptoms and severity* in asthmatic patients of all ages. They reduce airway hyperresponsiveness, frequency of exacerbations and improve quality of life in patients with asthma.
- It is the treatment of choice in *nocturnal asthma*, which is a manifestation of inflamed airways, reducing nocturnal awakening and reducing the diurnal variation in airway function.
- It is indicated in the *prophylactic treatment of asthma*. It reduces the prevalence and severity of exercise induced asthma.

It is *important to note* that steroids are of no value in the management of acute attacks and have no effect on early response to allergy or on mast cell mediator release but inhibit the late response due to eosinophils and macrophages.

Qd. What are the measures considered by the physician to reduce the incidence of side effects and improve treatment outcome, while prescribing inhaled corticosteroids for asthma control?

To minimize systemic availability of the drug and improve treatment outcome, the following measures are considered by the physician:

- The lowest effective dose of inhaled corticosteroid should be used. Add on therapies can reduce the dose of ICS required for asthma control, allowing a reduction in overall systemic exposure for most children with mild to moderate persistent asthma.
- It should be ensured that the patients can use their inhalers and know to comply with therapy.
- The use of a large volume spacer chamber should be advocated to reduce oropharyngeal deposition and therefore systemic absorption of corticosteroids is reduced.
- Patient should be educated to rinse the mouth and discard the rinse to minimize the swallowed drug.
- Selection of agents which have efficient first pass hepatic metabolism of the swallowed drug should be considered.

Qe. What are the advantages of using inhaled steroids over oral steroid therapy in the management of chronic bronchial asthma?

Inhaled steroids are widely used in the management of chronic bronchial asthma because of the following advantages:

1. Inhaled devices deliver the steroids directly to the airways achieving adequate target organ concentration at low dose. The amount of steroid inhaled is in micrograms which are units one thousand times smaller than the milligrams of steroid medication.
2. Inhaled steroids are *structurally modified* to facilitate topical absorption and minimize systemic effects.
3. Side effect profile of inhaled corticosteroids is better than oral steroids. Inhaled corticosteroids are less likely to cause serious side effects in adults when given in the usual doses. On the other hand, oral steroids when taken for many months or years harmful side effects are likely which consist of mood changes, forgetfulness, hair loss, easy bruising, a tendency towards high blood pressure and diabetes, thinning of the bones (osteoporosis), suppression of the adrenal glands, muscle weakness, weight gain, cataracts and glaucoma.

Qf. Although a significant proportion of the inhaled drug is deposited in the mouth and swallowed, systemic side effects occur rarely. Explain with reasons.

Systemic side effects occur rarely although a significant proportion of the inhaled drug is deposited in the mouth and swallowed because of the following reasons:

- Conversion of glucocorticoids to more lipophilic molecules through structural modifications such as esterification of the hydroxyl group at C17 or C21 positions, results in enhanced pulmonary drug absorption and reduced the risk of systemic side effects.
- High first pass metabolism is seen with fluticasone, mometasone and ciclesonide. This leads to reduced systemic absorption from the fraction of inhaled drug that is swallowed and consequently negligible oral bioavailability.

- Prodrugs (inactive analogues) such as beclomethasone and ciclesonide are converted into active metabolites by esterases in the lungs giving it a low bioavailability and high therapeutic index.

Qg. What are the local adverse effects you would expect in a patient on inhaled steroids? What instructions would you give to the patient to prevent them?

Inhaled steroids can suppress local immunity making the person more prone to infections such as oropharyngeal candidiasis. Deposition in the larynx leads to hoarseness of voice.

Local complications of inhaled corticosteroids can be avoided by rinsing the mouth each time after using an inhaler and by using a large volume spacer to capture large droplets of steroid that would be deposited in the oropharynx.

Qh. RY was prescribed leukotriene receptor antagonist for the initial management of signs and symptoms. What is the role of leukotriene pathway modifiers in the management of asthma? How do they act?

In patients with mild persistent asthma, who prefer to take oral medication than inhaled therapy, leukotriene pathway modifiers are the reasonable option.

Leukotrienes are potent bronchial smooth muscle constrictors. Leukotrienes C4 and D4 are approximately 1000 times more potent than histamine. Bronchial smooth muscle constriction by leukotrienes is considered a major cause of asthmatic symptoms. The synthesis and action of leukotrienes is modified in two ways:

i. Inhibition of 5-lipoxygenase, an enzyme, responsible for the synthesis of LTA4 from arachidonic acid by drugs such as zileuton.

ii. Antagonists of leukotrienes (LTC4, D4, E4) action on its receptors. Drugs include zafirlukast, montelukast.

Leukotriene pathway modifiers improve bronchial smooth muscle tone, reduce symptoms of wheezing and shortness of breath in asthma. They are used to treat allergies and relieve symptoms of hay fever. On long term use, these agents reduce the number of asthma attacks and improve control of asthma and reduce the need for beta-agonists.

Qi. In which formulations are they available and how do they offer advantage to the patient?

They are available as oral tablets rather than inhaled formulation.

The advantages of oral administration of leukotriene pathway modifiers are as follows:

- Easy mode of administration as compared to inhaled route which requires correct technique of use of inhalation device to ensure that the intended dose is delivered to the airways.
- Treats other coexisting allergic diseases such as hay fever, eczema, allergic rhinitis since the drugs are absorbed into the systemic circulation.

Qj. Is there a role for theophylline in treating patients with asthma? Explain.

Theophylline is inexpensive and widely available but its use has declined over time due to the following reasons:

- The development of newer antiasthma medications especially inhaled steroids and leukotriene modifiers.
- Low efficacy of theophylline compared to β2-agonist as bronchodilators.
- Increased frequency of side effects associated with theophylline because of its narrow therapeutic window.

- Inhibitors of cytochrome P450 enzymes inhibit metabolism of theophylline leading to clinically significant interactions.

Theophylline has a limited role as maintenance therapy for moderate to severe persistent when symptom control with inhaled corticosteroids alone is not adequate. The use of long-acting β2-agonists or leukotriene modifiers is preferred in this setting.

Qk. How does theophylline act?

Theophylline relaxes the smooth muscles of the bronchial airways causing bronchodilation. It exerts its effects through the following mechanisms:

- It acts as a competitive non-selective phosphodiesterase inhibitor which increases the concentration of intracellular cAMP accounting for the bronchodilator effect seen in asthma.
- It is also a non-selective adenosine receptor antagonist inhibiting the adenosine mediated bronchoconstriction. Adenosine induces the release of inflammatory mediators that are important in the pathogenesis of airway remodelling in asthmatics.
- Theophylline increases the release of interleukin-10, which has many anti-inflammatory effects.

Ql. Why monitoring of serum theophylline concentration is necessary?

Theophylline has a very narrow therapeutic window. The serum theophylline concentration requires monitoring to avoid toxicity as the adverse effects of theophylline are related to its plasma concentration and have been observed when plasma concentration exceeds 20 mg/L. At low plasma concentration, it fails to produce therapeutic effect.

Side effects can include headache, nausea, vomiting, irritability or hyperactivity, insomnia, and diarrhea. With higher serum theophylline levels, cardiac arrhythmias, seizures, and death can occur.

CASE 2: USE OF INHALED LONG-ACTING MUSCARINIC ANTAGONISTS (LAMA) IN BRONCHIAL ASTHMA

A 50-year-old male WL, is on medium dose inhaled corticosteroid and long-acting beta-adrenergic agonist (ICS/LABA) for maintenance and uses short-acting beta-adrenergic agonist (SABA) 1–4 times a week as reliever of symptoms.

Last year there were 2 exacerbations requiring short-term oral corticosteroid treatment. To reduce exacerbations, the treatment regimen was modified to high dose inhaled corticosteroid, long-acting beta-adrenergic agonist and long-acting muscarinic antagonist (ICS/LABA/LAMA). Tiotropium bromide was used as a long-acting muscarinic antagonist.

Qa. What is the scientific rationale for the use of long-acting muscarinic antagonists (LAMAs) in asthma?

The contractile tone of airways is controlled by the vagus nerve which releases acetylcholine. Increased acetylcholine receptor signalling through muscarinic receptors (M1, M2 and M3) play a role in increasing bronchoconstriction and also increase mucus secretion, inflammation, and airway remodelling, Long-acting muscarinic antagonists block acetylcholine signalling and prevent increased airway smooth muscle contractility induced by cholinergic tone.

Qb. Why is tiotropium bromide preferred over ipratropium bromide in managing asthma?

Acetylcholine mediated stimulation of M3 receptors causes bronchoconstriction and increased cholinergic tone. On the contrary, stimulation of presynaptic M2 receptor, acting as an autoreceptor, limits the release of acetylcholine and thus opposes the M3 mediated bronchoconstriction.

Ipratropium bromide blocks all subtypes of muscarinic receptors including presynaptic inhibitory M2 receptor. The non-selective blockade action on M2 receptors causes increased release of acetylcholine, that enhances the cholinergic tone of bronchial airways. This would counteract the desired bronchodilatory effect, resulting from antagonism of M3 receptors of airway smooth muscle. The therapeutic response is thus decreased with ipratropium bromide.

In contrast, tiotropium bromide shows high affinity and selectivity for M1 and M3 receptors with minimal affinity for M2 receptors. Its lower affinity for M2 receptors reduces its presynaptic effect to enhance the acetylcholine release. This leads to greater therapeutic efficacy with tiotropium bromide compared to ipratropium bromide.

Qc. Explain why atropine is not preferred for bronchial asthma treatment although it is a potent cholinergic antagonist.

Atropine can be used in the treatment of bronchial asthma but causes unwanted CNS effects, because it is a tertiary amine and readily crosses the blood–brain barrier. Tiotropium bromide and ipratropium bromide are quaternary ammonium compounds, so they do not cross the blood–brain barrier or produce CNS side effects. They have a superior side effect profile compared to atropine.

CASE 3: DRUGS FOR EXERCISE-INDUCED ASTHMA

Mr SK, a 21-year-old cricketer, playing at university level, comes with a history of shortness of breath while playing. There were three such attacks in the last 4 months, all of which were precipitated after exertion while playing or doing any vigorous exercise during fitness training.

There is no history suggestive of any cardiac or CNS or abdominal problem. There is also no previous history of bronchial asthma or valvular heart disease. Personal and family history is insignificant. Physical examination reveals no abnormality. The notes of the doctor who saw the patient during the attack revealed a hyper-resonant chest with bilateral rhonchi and prolonged expiratory sounds. Cardiovascular examination is normal.

He has a positive treadmill test for exercise-induced asthma (EIA).

Your diagnosis: Exercise-induced asthma (EIA).

Qa. Mention the drugs used for the prevention of exercise-induced asthma attacks in SK.

Short-acting β2-adrenergic agonists (SABAs) are generally the agents of choice for prophylaxis. For typical periods of exercise (e.g. <3 hours), pretreatment with agents such as albuterol 5 to 15 minutes before exercise usually provides excellent protection from exercise-induced asthma. For prolonged periods of exercise, long-acting β2-adrenergic agonists, LABAs (formoterol, salmeterol) provide several hours of protection.

Finally, the clinician should ensure that exercise is the only factor that precipitates asthma symptoms. If the clinical condition of the patient reveals persistent asthma or mild intermittent asthma beyond exercise-induced asthma, then long-term ICS or montelukast therapy should be started to reduce overall airway hyperresponsiveness.

CASE 4: OMALIZUMAB USE IN THE TREATMENT OF SEVERE ALLERGIC ASTHMA

A 20-year-old male KL, with severe persistent asthma, uncontrolled by inhaled corticosteroids and positive for perennial aeroallergens, was administered omalizumab 75 mg, SC, 2/weekly.

Qa. How is omalizumab useful in the management of allergic bronchial asthma as in case of KL?

Omalizumab is a monoclonal antibody that inhibits the binding of IgE to the IgE receptor on the surface of both mast cells and basophils. This limits the release of inflammatory mediators of the typical allergic response.

CASE 5: BENRALIZUMAB, A NEW TREATMENT APPROACH FOR SEVERE EOSINOPHILIC ASTHMA

A 35-year-old female TN, on high dose ICS/LABA and a LAMA for maintenance, has increased the use of SABA for the control of symptoms. Last year there were 3 exacerbations treated with oral corticosteroid bursts. Blood eosinophilia: 410 cells/µl.

Diagnosis: **Severe non-atopic eosinophilic asthma with frequent exacerbations, and prednisone responsive.**

Treatment prescribed: **Benralizumab was used as an add-on maintenance therapy for severe asthma at a dose of 30 mg, SC, first 3 doses 4 weekly, then 8 weekly.**

Qa. What is the rationale for prescribing benralizumab in the management of severe asthma in case of TN?

Benralizumab binds directly to the IL-5 receptor on eosinophil cells and blocks its signalling and the proliferation of IL-5 dependent cell lines. Benralizumab recruits natural killer cells, macrophages and neutrophils and triggers a magnified eosinophil apoptosis via antibody dependent cell-mediated cytotoxicity reducing blood, tissue and sputum eosinophil levels.

Benralizumab is used in select patients with eosinophilic asthma and plays a role in reducing acute exacerbations, improving the quality of life and decreasing mortality and disability.

Note: Mepolizumab binds to IL-5 and prevents IL-5 from binding to its receptor on the surface of eosinophils, thereby inhibiting eosinophil activation and proliferation.

CASE 6: ACUTE SEVERE ASTHMA (STATUS ASTHMATICUS)

A 52-year-old male asthma patient LK, on inhaled budesonide and formoterol was brought to the emergency in agitated state with severe respiratory distress following an episode of acute respiratory tract infection. On examination, she appears anxious, found to be sitting hunched forward and unable to speak in complete sentences.

Vital signs: **BP 110/62, pulse rate 130 bpm, respiratory rate 37 breaths/min, O_2 saturation 89% in room air and PEFR 45% of predicted.**

Diagnosis: **Acute severe asthma.**

Qa. How would you manage LK who is diagnosed as a case of acute severe asthma?

Acute severe asthma of LK can be managed as given below:

1. **Oxygen:** Oxygen therapy is essential with hypoxia being the leading cause of death of asthma. Oxygen therapy can be administered via a nasal canula or mask and titrated to maintain the patient's oxygen satuaration above 92%.
2. **Beta-2 agonists:** Rapid acting inhaled beta-2 agonist, typically albuterol is the first line therapy for acute asthma. It acts via stimulation of cyclic adenosine monophosphate-mediated bronchodilation. The airways are rich in beta receptors; the stimulation of

these receptors relaxes airway smooth muscles, increases mucociliary clearance, and decreases mucous production.

3. **Anticholinergics:** Ipratropium bromide is the anticholinergic agent of choice and its action can be synergistic with albuterol or other beta-2 agonists, when treating severe acute asthma exacerbations.
4. **Steroids:** Glucocorticoids are the most important treatment for status asthmaticus. IV hydrocortisone 100 to 200 mg is used because it has a rapid onset of action. Methyl prednisolone is selected in a patient with heart disease as it has less mineralocorticoid action and water retention action. Intravenous hydrocortisone hemisuccinate at a dose 4 mg/kg body weight, may be given at intervals of 140 minutes. Hypokalemia may result from large doses of intravenous corticosteroids and potassium supplements are recommended.

   Corticosteroid action usually requires at least 4–6 hours to occur following corticosteroid administration because protein synthesis is required before the initiation of a corticosteroid's anti-inflammatory effects. Because of this, patients with status asthmaticus must depend on other supportive measures (e.g. beta-2 agonists, oxygen, adequate ventilation).
5. **Aminophylline:** The popularity of aminophylline use in asthma exacerbations has diminished in recent years.
6. **Magnesium sulphate:** Magnesium has a role in smooth muscle relaxation, inhibition of histamine release and acetylcholine release from nerve endings. When the patient is not responding to bronchodilator therapy, magnesium sulphate may be used.

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Section III

Disorders of the Cardiovascular System

3. Antihypertensive Drugs
4. Drug Therapy for Angina Pectoris
5. Antithrombotic Therapy and Drugs for Myocardial Infarction
6. Drugs for Heart Failure
7. Antiarrhythmic Drugs

Chapter

3

Antihypertensive Drugs

CASE 1: THIAZIDES THERAPY IN GRADE I AND LOW RISK HYPERTENSION

PQ, a 50-year-old female, BMI 24.3 kg/m^2 undergoes routine annual health check up. Systemic examination and other laboratory tests were within normal limits. Her blood pressure reading showed 148/95 mm of Hg.

The patient is advised lifestyle modification for 6 months. Thereafter, when the blood pressure failed to normalise, she was prescribed drug therapy, tab. hydrochlorothiazide, 25 mg orally once daily.

Qa. Mention the advantages of hydrochlorothiazide (thiazide diuretics), prescribed for PQ in the management of hypertension.

Thiazide diuretics have the following advantages in the management of hypertension:

- Thiazide diuretics have good oral bioavailability and long duration of action. They can be administered once daily and do not require dose titration.
- They have additive or synergistic action when combined with other classes of antihypertensive agents.
- Thiazides are efficacious as other class of antihypertensive agents.
- They are well tolerated as the adverse effects are few and infrequent.
- They are inexpensive and cost effective when used in long term for the treatment of hypertension.

Qb. What is the mechanism involved in lowering of blood pressure with thiazide diuretics?

Initial antihypertensive effect is seen due to a decrease in extravascular volume. Thiazides interact with NaCl cotransporter expressed in the DCT in the kidney, enhancing Na^+ excretion in the urine leading to a decrease in cardiac output and fall in blood pressure.

In long term, this hypotensive effect is maintained due to the action of thiazide diuretics on Ca^{2+} activated K^+ channels mediating K^+ efflux, causing hyperpolarization and closure of L type Ca^{2+}channel reducing the entry of Ca^{2+}. Thus, there is *decrease in the systemic vascular resistance* which in turn causes a fall in blood pressure.

Qc. What are the possible metabolic side effects associated with thiazide diuretics prescribed for hypertension?

Latent diabetes mellitus may be unmasked during therapy with thiazide diuretics. Thiazide-induced impairment of glucose tolerance is due to both, reduced glucose stimulated insulin release and increased peripheral resistance to the actions of insulin.

Elevated insulin levels may cause hypertriglyceridaemia, increased plasma levels of low density lipoprotein (LDL) and cholesterol while decreasing plasma levels of high density lipoproteins (HDL).

CASE 2: CALCIUM CHANNEL BLOCKER AND ACE INHIBITOR THERAPY IN THE MANAGEMENT OF HYPERTENSION

SK, a 45-year-old male, attended the clinic with complaints of headache, fatigue and insomnia. He is a known case of diabetes for 5 years and blood glucose level is controlled on insulin therapy. On examination, his blood pressure readings are 152/95 mmHg. Oher laboratory tests were within normal limits. He was prescribed combination therapy with ACE inhibitor and calcium channel blocker.

Qa. Which are the drugs available for the treatment of hypertension?

The antihypertensive drugs can be classified as follows:

Sl. No	*Class*	*Drugs*
I	**Diuretics**	• *Thiazide diuretics*: Hydrochlorthiazide, chlorthalidone, indapamide • *Loop diuretics:* Furosemide, torsemide, bumetanide • *K^+ sparing diuretics*: Spironolactone, triamterene, amiloride
II	**Sympatholytics**	• *Central sympatholytics*: Clonidine, methyldopa • *Ganglion blockers*: Trimethaphan • *α1-adrenergic antagonists*: Prazosin, terazosin, doxazocin, phenoxybenzamine, phentolamine • *β1-adrenergic antagonists:* Atenolol, bisoprolol, metoprolol • *β + α-blockers*: Labetalol, carvedilol
III	**Calcium channel blockers**	• Nifedipine, amlodipine, felodipine, nicardipine, clevidipine, diltiazem, verapamil
IV	**Vasodilators**	• *Arteriolar dilators*: Hydralazine, minoxidil, diazoxide, fenoldopam • *Arteriolar + Venous dilators*: Sodium nitroprusside
V	**Renin–Angiotensin System Blockers**	• *Angiotensin: Converting enzyme inhibitors*: Enalapril, lisinopril, ramipril, quinapril, benazepril • *Angiotensin receptor antagonists:* Losartan, valsartan, telmisartan, irbesartan

Qb. How would you grade hypertension according to European guidelines (ESC/ESH guidelines) 2018, in case of SK considering his risk factors and blood pressure readings of 152/95 mmHg?

The patient SK has blood pressure values of 152/95 mmHg and is a known case of diabetes, which is a risk factor for cardiovascular disease (CVD). Hence, his hypertension is classified as **'grade I and high risk'.**

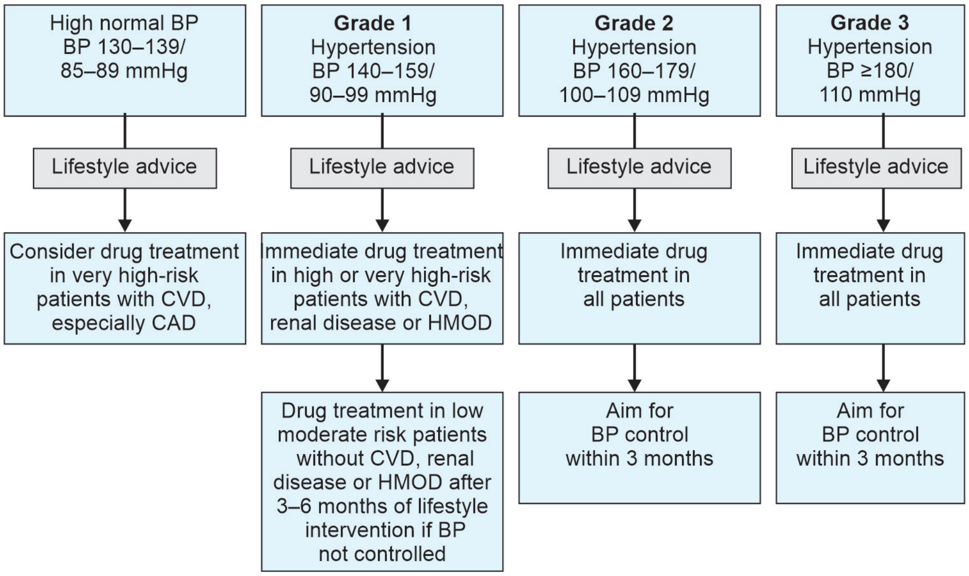

High normal BP
BP 130–139/
85–89 mmHg
Grade 1
Hypertension
BP 140–159/
90–99 mmHg
Grade 2
Hypertension
BP 160–179/
100–109 mmHg
Grade 3
Hypertension
BP ≥180/
110 mmHg
Lifestyle advice
Lifestyle advice
Lifestyle advice
Lifestyle advice
Consider drug treatment in very high-risk patients with CVD, especially CAD
Immediate drug treatment in high or very high-risk patients with CVD, renal disease or HMOD
Immediate drug treatment in all patients
Immediate drug treatment in all patients
Drug treatment in low moderate risk patients without CVD, renal disease or HMOD after 3–6 months of lifestyle intervention if BP not controlled
Aim for BP control within 3 months
Aim for BP control within 3 months

Fig. 3.1: ESC/ESH Hypertension grading and treatment guidelines

Qc. What are the therapeutic goals in the management of hypertension? How is hypertension managed in case of SK considering the ESC/ESH guidelines 2018?

It is recommended that the objective of treatment should be to lower BP to <140/90 mmHg in all patients and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients.

Immediate antihypertensive drug treatment is recommended alongside lifestyle intervention for patients with **grade I and high risk** hypertension.

Qd. When would you prefer combination therapy in the management of hypertension? Is it appropriate to initiate therapy as a two-drug combination in case of SK?

Initial combination therapy is recommended for patients with *grade 2 or 3 hypertension.* Also grade I hypertension in young patients (<65 years) with an initial SBP >150 mmHg who would require BP reduction of ≥20 mmHg combination therapy is preferred. In other words, initial monotherapy is recommended for grade 1 hypertension and low or moderate risk patients and in frail older patients.

In case of SK SBP value is 152 mmHg (≥150 mmHg) and he is diabetic (high risk). The therapeutic goal is to reduce BP to <130/85 mmHg. Thus, a two-drug combination therapy would be more effective in controlling blood pressure than monotherapy.

Qe. How is combination therapy better than single drug in the management of hypertension?

The advantages of two-drug combination therapy versus monotherapy are the following:

- *Effectiveness:* Initial low dose combination therapy is invariably more effective at blood pressure lowering than high dose monotherapy.
- *Adverse effects:* Combination therapy will limit potential adverse effects associated with monotherapy, e.g. reduced risk of hypokalemia due to diuretic and reduced prevalence of peripheral edema due to calcium channel blockers.

- *Blood pressure, a multiregulated variable,* depends on many compensating pathways. Combination of drugs, working through different mechanisms regulate blood pressure better than monotherapy, acting through one pathway.
- *Synergistic or additive antihypertensive* effect of combination therapy, e.g. combination of β-blocker and a thiazide diuretic results in additive hypertensive effect that permits the effective use of very low doses of thiazides.
- *Complementary mechanism of action of drugs*, e.g. β-blocker combined with thiazide diuretics. Thiazide diuretics induce increased sympathetic outflow and renin angiotensin axis activation which is blunted by β1-adrenergic blockade.

Case Continued

SK was prescribed single pill combination of angiotensin converting enzyme inhibitor (ramipril) and Ca^{2+} channel blocker (amlodipine).

Qa. Is the combination of angiotensin converting enzyme inhibitor (ACEI) and calcium channel blockers (CCB), prescribed in case of SK, a rational combination? If yes, justify.

Yes, the combination of angiotensin converting enzyme inhibitor (ACEI) and calcium channel blocker (CCB) is a rational combination.

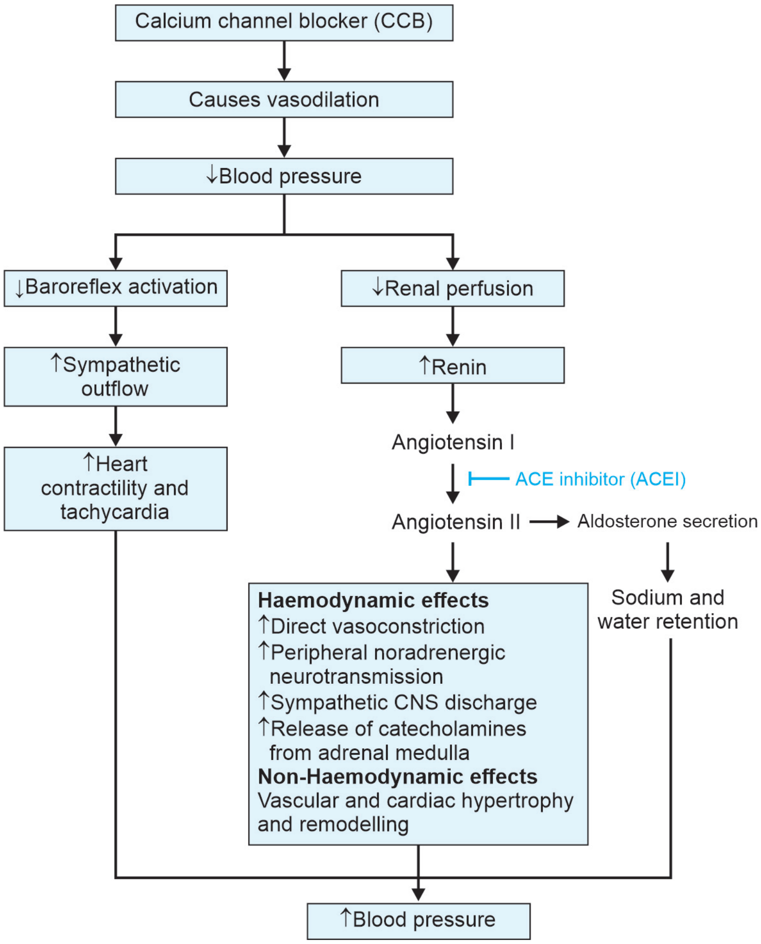

Calcium channel blocker (CCB)
Causes vasodilation
↓Blood pressure
↓Baroreflex activation
↓Renal perfusion
↑Sympathetic outflow
↑Renin
↑Heart contractility and tachycardia
Angiotensin I
ACE inhibitor (ACEI)
Angiotensin II
Aldosterone secretion
Sodium and water retention
Haemodynamic effects
↑Direct vasoconstriction
↑Peripheral noradrenergic neurotransmission
↑Sympathetic CNS discharge
↑Release of catecholamines from adrenal medulla
Non-Haemodynamic effects
Vascular and cardiac hypertrophy and remodelling
↑Blood pressure

Fig. 3.2: Effects of combination therapy with calcium channel blocker and ACE inhibitor

CCBs act by causing vasodilation associated with a fall in the blood pressure. Subsequent to fall in blood pressure, there is reflex activation of sympathetic system and renin angiotensin system leading to unwanted tachycardia, volume expansion and other deleterious effects on the heart, blood vessels and kidney. ACE inhibitor combined with a calcium channel blocker (CCB) acts *synergistically to produce blood pressure lowering in small doses and prevent structural damage* to heart, blood vessels and kidney.

ACE inhibitors have been shown to reduce albuminuria and the appearance or progression of diabetic nephropathy. They also reduce the incidence of cardiovascular events in patients with diabetes and other high risk factors, producing beneficial effects.

In terms of *side effects*, ACE inhibitors and calcium channel blockers are devoid of metabolic and central nervous system adverse effects. Combining an ACE inhibitor with CCB reduces the incidence of peripheral edema which is a common side effect of CCB.

These combinations are *available as a single pill and in a range of doses*. This facilitates simplification of treatment, improvement in treatment adherence, flexible prescribing and up titration from lower to higher doses.

Qb. How does nifedipine act as blood pressure lowering agent in a hypertensive patient? What is the effect of nifedipine on the heart rate of an individual treated for hypertension?

Nifedipine has selective and pronounced action on smooth muscle of blood vessels particularly the arterial blood vessels with minimal effect on venous blood vessels. It lacks significant effect on cardiac muscle.

Ca^{2+} influx through L type calcium channels plays an important role in determining vascular tone in smooth muscle and cardiac contractility. Decreased Ca^{2+} entry through the L type Ca^{2+} channels lowers the intracellular Ca^{2+} concentration. This reduces the Ca^{2+} calmodulin mediated activation of myosin light chain kinase and phosphorylation of myosin light chain. Thus, the interaction between actin and myosin filament is reduced. This results in reduced systemic vascular resistance and fall in arterial blood pressure.

$$\text{MAP} = \text{SVR} \times \text{CO}$$

Nifedipine causes a significant fall in blood pressure and this elicits a baroreceptor reflex mediated increased sympathetic discharge producing unwanted side effects such as *tachycardia and palpitation*.

Qc. Explain why amlodipine is preferred over nifedipine in the treatment of hypertension.

Amlodipine has slow absorption which allows a gradual rise in plasma concentration and late peak plasma concentration. It has high binding affinity with the cell membranes which contribute to slow hepatic metabolism. This accounts for its long plasma half-life of 35 to 50 hours with minimal peaks and troughs in plasma concentration. There is less reflex tachycardia compared to nifedipine which causes dramatic fall in blood pressure and rapid heart rate.

Qd. Among the dihydropyridine calcium channel blockers, which calcium channel blocker is preferred in the following clinical settings?

i. **Angina:** *Nicardipine* has selected for coronary blood vessels. They preferentially dilate the coronary blood vessels increasing the coronary blood flow and myocardial oxygen supply. This is useful in the treatment of angina.

ii. **Subarachnoid haemorrhage:** *Nimodipine* has high lipid solubility, easily crosses the blood–brain barrier, relaxes the cerebral blood vessels and treats cerebrospasm associated with subarachnoid haemorrhage.

iii. **Hypertensive emergency:** *Clevidipine* has a short half-life of 2 minutes and rapid onset and offset of action as it is metabolised by esterases in blood. It preferentially effects the arterial smooth muscle with less action on veins. It is available for intravenous administration in the treatment of hypertensive emergencies or perioperative hypertension when oral therapy is not possible or desirable.

Qe. Explain why ACE inhibitors and ARBs are contraindicated in bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney.

In bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney the perfusion to the kidney decreases. In such circumstances, the vasoconstrictor effect of angiotensin II on the efferent arteriole predominates which increases GFR and thus plays an autoregulatory role in preserving glomerular filtration through an increase in post-glomerular resistance. Suppression of angiotensin II formation with an ACE inhibitor can cause a critical reduction in glomerular filtration and increase the chances of renal failure.

Case Continued

Mr SK, within a few months of initiating treatment with ACE inhibitor and CCB, the blood pressure stabilised but he developed dry cough which did not subside with cough suppressants or antibiotics. He goes to the physician who suspects that the cough is due to ACE inhibitor.

Qa. What is the underlying mechanism for ACE inhibitor-induced cough? What should be the line of treatment?

Chronic cough can occur with ACE inhibitors, which is typically dry with a tickling or scratching feeling in the throat. The mechanism underlying ACE inhibitor-induced cough are probably linked to inhibition of ACE enzyme which degrades bradykinin and substance P resulting in accumulation of these mediators in the respiratory tract leading to cough.

ACE inhibitor-induced cough is independent of dose and is a class effect. As it can happen with all other agents of the class, it is necessary to switch to an angiotensin receptor blocker (ARB) or to some other class of antihypertensive drug.

CASE 3: BETA-BLOCKER THERAPY IN THE MANAGEMENT OF HYPERTENSION

A 58-year-old female RY was treated with tablet metoprolol 12.5 mg twice daily for hypertension. He is a known case of ischaemic heart disease and diabetes mellitus on insulin therapy. There is no history of reactive airway disease.

Qa. Given that RY is prescribed metoprolol, a beta-blocker, for the management of hypertension, mention the mechanisms through which beta-blockers lower blood pressure.

Mechanisms by which β-blockers produce reduction in blood pressure are the following:

- Blockade of cardiac β1-receptors reduces contractility (negative inotropic effect) and heart rate (negative chronotropic) and subsequently decrease stroke volume and cardiac output which accounts for initial anti-hypertensive effect.
- Blockade of β1-receptors in JG apparatus in renal cortex reduce renin secretion, thereby decreasing the production of angiotensin II, a potent vasoconstrictor of blood vessels and lower blood pressure through reduction in systemic vascular resistance on long-term therapy.
- Nebivolol is a β1-selective adrenergic antagonist that also promotes vasodilation via activation of nitric oxide pathway.

- Labetalol is mixed α–β-antagonist, available in oral and intravenous formulations. It decreases blood pressure by reduction of systemic vascular resistance via antagonism of α1-receptors. The reflex rise in heart rate or cardiac output is not seen because cardiac β1-receptors are also antagonized.

Qb. Caution should be considered when prescribing beta-blockers in hypertensive patients with diabetes receiving insulin therapy. Explain with reasons.

Treatment with beta-blockers, in diabetic patients on insulin therapy, can cause prolongation or worsening of hypoglycaemia, due to interruption in sympathetic compensatory mechanisms in response to hypoglycaemia.

1. The sympathetic regulation of hepatic glucose production by β2-mediated glycogenolysis and gluconeogenesis, which restores blood glucose levels in hypoglycaemia is impaired, in presence of non-selective beta-blocker.
2. Sympathetic nervous system mediated release of glucagon from alpha cells of pancreas in response to fall in blood glucose is inhibited.
3. The neurogenic symptoms (hunger, anxiety, palpitation, tremor, pallor, sweating, paresthesias) are the results of the physiologic changes caused by the autonomic nervous system's response to hypoglycaemia. This warns the patient to eat sugar. Beta-blockers mask these symptoms and delay recovery from hypoglycaemia. Hence incipient hypoglycaemia may go unnoticed by the patient who may suffer from hypoglycaemic coma.
4. Beta-blockers particularly non-selective beta-blockers may also predispose to significant hypertension during hypoglycaemia due to unopposed vascular alpha adrenergic stimulation.
5. Non-selective beta-blockers (e.g. propranolol) increase TG levels and lower HDL-C levels without affecting LDL-C levels which can give rise to dyslipidaemia.

Therefore, beta-blockers should be administered with caution in patients receiving insulin therapy and oral hypoglycaemic drugs and blood glucose monitoring should be done frequently to detect changes in blood glucose. Cardioselective beta-blockers (e.g. atenolol and metoprolol) are relatively safer than non-selective beta-blockers and are preferred for treatment.

Qc. Why is abrupt withdrawal of beta-blocker not encouraged? How can we withdraw beta-blocker, used as chronic therapy for hypertension?

Chronic therapy with beta-blockers is associated with upregulation in the number of beta-receptors or supersensitivity of beta-receptors. These newly formed beta-receptors show hyper responsiveness to even smaller release of catecholamines. Therefore, abrupt withdrawal of beta-blocking drugs in patients with hypertension, results in transient symptoms including headache, malaise, sweating, palpitations and increases in blood pressure. Hence, there should be gradual tapering of the doses instead of abrupt withdrawal with regular monitoring of blood pressure to prevent rebound hypertension.

Qd. Why is it important to rule out coexisting bronchial asthma with hypertension prior to prescribing beta-blockers?

Beta-2 agonists provide relief of acute symptoms of bronchial asthma through stimulatory action at β2-receptors of bronchial smooth muscle, which mediate bronchodilation, and therefore serve as mainstay therapy.

Non-selective beta-blockers, may negatively affect the reduced basal lung function in patients with bronchial asthma by preventing β2-mediated bronchodilation, and may precipitate acute bronchospasm leading to exacerbation of asthma. Thus, they diminish the effectiveness of beta-agonist drugs, commonly used for the treatment of bronchial asthma.

Qe. How are cardioselective beta-blockers better than non-selective beta-blockers in the treatment of hypertension with bronchial asthma?

Cardioselective beta-blockers such as atenolol and metoprolol are approximately 20 times more potent at blocking β1-receptors than β2-receptors. At therapeutic doses, the β2-blocking effect is minimal and therefore the risk of bronchoconstriction is negligible. In contrast, non-selective β-blockers have been reported to cause increased bronchospasm and severe asthma exacerbation.

Qf. Which antihypertensive drugs would you select for the management of hypertension, in a patient with bronchial asthma?

The management of hypertensive patient with asthma should include lifestyle changes, among which cessation of smoking is essential.

Calcium channel blockers (CCBs), ARBs or ACE inhibitors or CCB/RAS blocker combination are recommended as initial drugs of choice.

If the blood pressure response is poor, or depending on other comorbidities, thiazides or thiazide-like diuretics and beta-1 selective beta-blockers can be considered.

CASE 4: DRUG THERAPY OF ISOLATED SYSTOLIC HYPERTENSION

BK, a 70 years elderly female, presented to the geriatric OPD with isolated systolic hypertension of 150/85 mmHg.

Qa. How do you define 'isolated systolic hypertension' (ISH)? Which drugs would you select for the management of systolic blood pressure in elderly?

Isolated systolic hypertension (ISH) is defined as systolic blood pressure > 140 mmHg and diastolic blood pressure < 90 mmHg. ISH increases the risk of stroke, other CV diseases and death.

Treatment of isolated systolic hypertension with diuretics, calcium channel blockers (CCBs), and angiotensin II inhibitors, is effective in reducing systolic blood pressure, preventing cardiovascular morbid events, and lowering mortality. These agents may have to be used in combination to achieve the systolic blood pressure goal of < 140 mmHg.

CASE 5: DRUG THERAPY FOR HYPERTENSION IN PREGNANCY

A 30-year-old pregnant woman KL came to antenatal clinic for routine check-up at 25 weeks of gestation. Her blood pressure was found to be increased to 156/105 mmHg and she was prescribed methyldopa. There is no history of use of antihypertensive medications in the past.

Qa. You have diagnosed KL as a case of 'gestational hypertension'. How do you differentiate gestational hypertension from chronic hypertension?

Chronic hypertension is defined as blood pressure exceeding 140/90 mmHg before pregnancy or before 20 weeks gestation. When hypertension is first identified during a woman's pregnancy and she is at less than 20 weeks gestation, blood pressure elevations usually represent chronic hypertension. In contrast, new onset of elevated blood pressure readings after 20 weeks of gestation without problems in the kidneys or other organs indicate gestational hypertension. Some women with gestational hypertension may develop pre-eclampsia.

Qb. Which drugs would you select to treat hypertension in pregnancy?

Anti-hypertensive drugs which are safe in pregnancy and could be used for treatment of hypertension in pregnancy are intravenous labetalol, oral methyldopa or calcium channel blocker.

CASE 6: DRUG THERAPY FOR HYPERTENSION WITH CHRONIC KIDNEY DISEASE

A 50-year-old male TN is suffering from chronic renal disease with moderate hypertension.

Qa. Which drugs will you prescribe to control hypertension in case of TN with coexisting renal dysfunction?

Patients with CKD should receive lifestyle advice, especially sodium restrictions. Combination therapy should be initiated with a RAS blocker with a CCB or diuretic in these patients. Loop diuretics should replace thiazide diuretics when the estimated GFR is < 30 ml/min.

Qb. Which drugs would you select for the treatment of hypertensive emergency with acute renal failure?

The drugs of choice in treating patients with hypertensive emergency and acute renal failure are clevidipine, fenoldopam, and nicardipine.

CASE 7: DRUG THERAPY OF HYPERTENSIVE CRISIS SECONDARY TO PHEOCHROMOCYTOMA

LM, a 40-year-old male patient, presented to the tertiary care hospital, with symptoms of headache, dizziness, sweating, palpitation and tremor. He was diagnosed with hypertension one year ago and treatment was initiated with tab chlorothiazide. In spite of his current medication, blood pressure is not under control. On evaluation, BP values are 220/120 mmHg, 24-hour urine analysis showed high levels of metanephrines and catecholamines.

Diagnosis of pheochromocytoma hypertensive crisis was confirmed and surgical resection of tumour was planned.

Phenoxybenzamine (α-blocker) was initiated 12 days prior to operation of the tumour.

Qa. What are the signs and symptoms that are consistent with the diagnosis of pheochromocytoma? Which drugs are used for the treatment of pheochromocytoma hypertensive crisis?

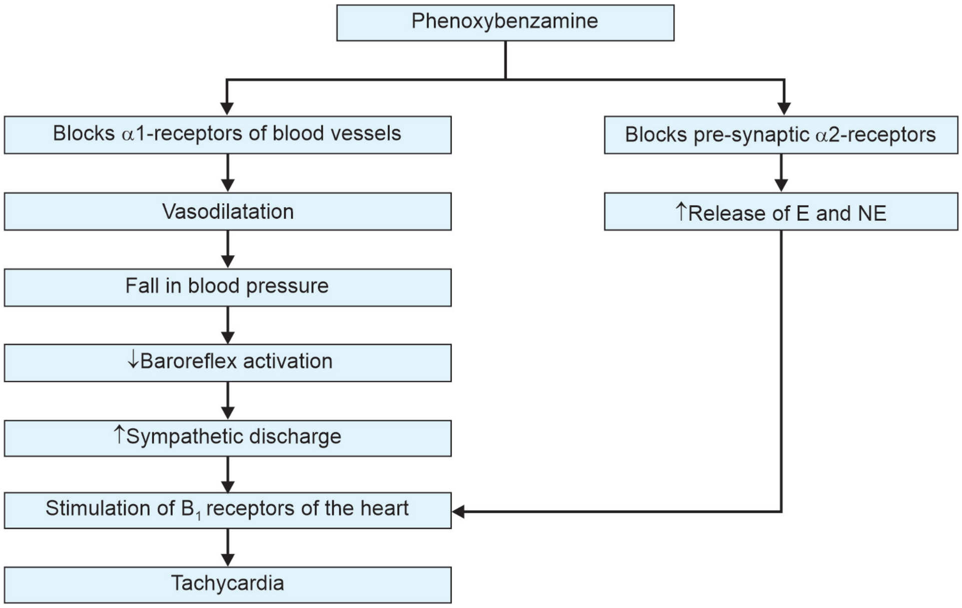
The patient is suspected of having pheochromocytoma, a tumour of adrenal medulla which secretes excess catecholamines leading to symptoms of sweating, palpitation, tremor and raised blood pressure. In spite of his current medications, blood pressure is not under control. Laboratory tests show high levels of metanephrines and catecholamines in urine.

Drugs of choice for treating hypertensive emergency due to pheochromocytoma are intravenous clevidipine, nicardipine or phentolamine.

Qb. How does phenoxybenzamine act to control blood pressure? What is its effect on heart rate, when used in hypertension associated with pheochromocytoma as in case of LM?

Phenoxybenzamine blocks both $\alpha 1$ and $\alpha 2$-adrenergic receptors with more affinity for $\alpha 1$-receptor, leading to vasodilatation and low systemic vascular resistance causing a fall in the blood pressure.

The fall in blood pressure, *results in reduced activation of baroreceptor reflex mechanisms causing increased sympathetic discharge.* The sympathetic discharge is further enhanced by *non-selective blockade of inhibitory presynaptic α2-receptors* by phenoxybenzamine, causing excess neuronal release of norepinephrine. Since α1-receptors are blocked, the catecholamines predominantly *stimulate β1-receptors of the heart* producing tachycardia and palpitation.


Phenoxybenzamine
Blocks α1-receptors of blood vessels
Blocks pre-synaptic α2-receptors
Vasodilatation
↑Release of E and NE
Fall in blood pressure
↓Baroreflex activation
↑Sympathetic discharge
Stimulation of B_1 receptors of the heart
Tachycardia

E: Epinephrine, NE: Norepinephrine

Fig. 3.3: Effect of phenoxybenzamine on blood pressure and heart rate

Qc. Why phenoxybenzamine is initiated 12 days prior to operation of the pheochromocytoma tumour?

Pheochromocytomas are catecholamine-producing neoplasms, that can cause life-threatening haemodynamic instability, particularly intraoperatively, when the tumour is manipulated. The goal of preoperative treatment with phenoxybenzamine is to *prevent a sudden release of catecholamines or attenuate the response to a release of catecholamines perioperatively,* thus lowering the risk of developing dangerously high blood pressure during surgery.

Qd. Why phenoxybenzamine use is favoured over selective alpha-antagonists in the management of pheochromocytoma?

Phenoxybenzamine is a haloalkylamine derivative. The molecular structure responsible for blockade is the highly reactive carbonium ion formed by cleavage of the tertiary amine ring. It forms *stable covalent bond with α-adrenergic receptors, resulting in non-competitive and irreversible blockade*, not allowing adrenaline and noradrenaline to bind with the α-receptors. This leads to *long duration of action* which allows twice daily dosing and prevents excess catecholamine action on α-adrenergic receptors. Thus phenoxybenzamine is useful in the treatment of catecholamine secreting pheochromocytoma tumour.

Qe. What is the therapeutic objective of adding beta-blocker to alpha blocker in the management of the patient LM?

The therapeutic objective of adding beta-blocker to alpha-blocker in the medical management of the patient LM are the following:

- To control β1-mediated tachyarrhythmias which may occur following phenoxybenzamine administration.
- Beta-blocker in combination with alpha-blocker act synergistically in lowering blood pressure and in the management of hypertensive crisis.

Qf. Explain why beta-blockers are not initiated without adequate alpha blockade, for the management of pheochromocytoma.

In pheochromocytoma, tumour of adrenal medulla causes excess secretion of adrenaline and noradrenaline. The actions of adrenaline are on both α and β-receptors. If β-blockers are added prior to α-blocker, blockade of vasodilatory effect of β2-receptors in blood vessels would *result in unopposed α1-receptor mediated intense vasoconstriction*. This *nullifies the beta-blocker induced reduction in blood pressure* and may also lead to hypertensive crisis due to excessive stimulation of α1-adrenergic receptors with catecholamines. Therefore, beta-blockers should be added only after adequate alpha blockade.

Qg. How does phentolamine help in the diagnosis of pheochromocytoma and why is phentolamine chosen for this purpose?

Phentolamine test can be performed to diagnose pheochromocytoma-induced hypertension. If after giving 5 mg of phentolamine IV, the blood pressure falls by 25 to 35 mmHg, it is a case of pheochromocytoma. If the fall in blood pressure is less, it is a case of essential hypertension.

Among the alpha-blockers phentolamine is selected for the test because it has a *rapid onset of action and short duration of action*.

CASE 8: DRUG THERAPY FOR HYPERTENSION WITH BENIGN HYPERPLASIA OF PROSTATE

A 58-year-old male RX was diagnosed to have benign prostatic hyperplasia one year ago. He was prescribed tamsulosin for treatment of his urinary symptoms. He returns to surgery OPD for his routine check-up. He reports that he is relieved of his urinary symptoms but complains of headache and sleep disturbances. On examination his blood pressure was found to be elevated (150/95 mmHg). There is no history of use of antihypertensive medications in the past.

The surgeon substituted terazosin for tamsulosin and counselled RX that terazosin will control his blood pressure and also his urinary symptoms.

Qa. What is the rationale for replacing tamsulosin with terazosin in case of RX?

Terazosin has a long duration of action, is administered once daily and is *effective in treating both hypertension and the symptoms of enlarged prostate*. The blood pressure lowering effect is due to *blockade of α1-receptors of the smooth muscle of blood vessels* and relief of urinary symptoms is due to *antagonistic effect at α1-receptors in the smooth muscle of bladder neck, sphincter and urethra,* thus reducing the resistance to urinary flow. Additionally, terazosin improves lipid profile and is useful in dyslipidaemia.

Therefore, terazosin is considered to be a suitable alternative to tamsulosin because tamsulosin is effective in the *treatment of urinary symptoms of benign hyperplasia of prostate with a little or no effect on blood pressure*. This is due to selectivity of tamsulosin for *α1a-receptor* subtype which is predominant in the prostate, bladder neck and urethra, but not in blood vessels.

Qb. What is the advantage of terazosin, a selective alpha blocker over non-selective alpha blockers, as an antihypertensive agent?

Non-selective alpha-blockers produce *unwanted tachycardia and palpitation* due to *blockade of presynaptic α2-receptors* causing release of adrenaline and noradrenaline from the adrenergic nerve terminals, which act on β1-receptors of the heart causing tachycardia and palpitation.

Terazosin has selective action on α1-receptors with subsequent lowering of blood pressure without causing tachycardia. Therefore, terazosin is an effective antihypertensive agent and better safety profile compared to non-selective alpha-blockers.

Qc. Mention the most likely side effect associated with terazosin use. How can the side effect be prevented?

The most common intolerable side effect of terazosin is *marked postural hypotension, especially at first dose, also known as first dose hypotension.* There can be sudden drop in blood pressure which could lead to dizziness or fainting.

Treatment with terazosin is initiated at a low dose and gradually the dose is increased depending on the blood pressure. To avoid injury related to dizziness or fainting, the first dose is advised to be taken at bedtime to reduce the risk of postural hypotension.

CASE 9: DRUG THERAPY OF HYPERTENSIVE EMERGENCIES WITH ASSOCIATED CLINICAL CONDITIONS

A 63-year-old woman, KT, with a long history of hypertension and diabetes is brought to the emergency department by relatives with complains of severe headache, left-sided weakness and has become incoherent over the past 24 hours.

Physical examination reveals a disoriented woman whose blood pressure is 230/160, respiratory rate is 25, and pulse is 110. The patient is afebrile. He has papilloedema and weakness, numbness in face, arm and leg on the left side.

There is history of not taking her antihypertensive medicines in the past several weeks. CT scan reveals no evidence of haemorrhage or mass lesion.

Qa. How do you differentiate between hypertensive emergency and hypertensive urgency? To which of these two categories would you classify the patient KT?

Hypertensive emergency (HE)	*Hypertensive urgency (HU)*
Blood pressure greater than 180/120 mmHg *in the presence of impending or progressive organ damage*	Blood pressure greater than 180/120 mmHg without acute organ damage.
Examples include hypertensive encephalopathy, cerebral infarction, intracerebral haemorrhage, myocardial ischaemia or infarction, pulmonary edema, aortic dissection, eclampsia, acute renal insufficiency	Patient often is asymptomatic, may present with headache, shortness of breath, epistaxis or anxiety
Requires parenteral anti-hypertensive agents	Requires intensification of drug therapy

This is a possible case of *transient ischaemic attack,* with symptoms of difficulty in speech, numbness on one side of the body and blood pressure greater than 180/120 mmHg, requiring parenteral anti-hypertensive agents. Therefore, KT is a case of 'hypertensive emergency'.

Qb. Mention the antihypertensive drugs which are selected in the following clinical situations.

Clinical situation	*Drugs of choice*
I. Hypertensive emergency (HE) with acute aortic dissection	Esmolol
II. HE with acute pulmonary edema	Nitroglycerine Clevidipine, nitroprusside
III. Hypertension with acute myocardial infarction	Esmolol, nitroglycerine
IV. HE and acute intracerebral haemorrhage	Clevidipine, nicardipine Labetalol, urapidil
V. HE caused by pheochromocytoma, hyperadrenergic state caused by cocaine, amphetamine or MAO inhibitor or by abrupt cessation of clonidine or other sympatholytic drugs	Clevidipine, nicardipine Phentolamine
VI. Postoperative surgical hypertension	Clevidipine, esmolol Nicardipine, nitroglycerine
VII. Hypertensive crisis with eclampsia or pre-eclampsia	Hydralazine, labetalol, nicardipine
VIII. HE with acute renal failure	Clevidipine, fenoldopam Nicardipine

Qc. Outline the management of hypertensive emergency in case of KT.

The primary aim of therapy should be immediate lowering of arterial pressure even before the results of all laboratory tests are available.

- The initial goal in hypertensive emergencies is to reduce blood pressure by 25% of presentation baseline within the first 2 hours, then towards 160/100 mmHg within the next 4 hours. Overzealous blood pressure reduction may lead to coronary, cerebral or renal ischemia.
- Use of potent parenteral anti-hypertensives which have rapid onset and short duration of action are the preferred agents. *Sodium nitroprusside* is the drug of choice for most hypertensive emergencies. It reduces blood pressure rapidly, is readily titratable and its action terminates rapidly when discontinued. However, the administration of this agent by continuous intravenous infusion requires continuous monitoring of arterial blood pressure. Cyanide toxicity associated with sodium nitroprusside may occur in hepatic impairment and renal insufficiency.
- *Diazoxide* can be used in situations where arterial monitoring is not available. However, the use of diazoxide may be complicated by hypotension and tachycardia, thereby causing exacerbation of myocardial ischemia.
- *Intravenous labetalol, a titratable beta-blocker, and intravenous nicardipine, a calcium channel antagonist,* may prove to be acceptable alternatives.

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Chapter

4

Drug Therapy for Angina Pectoris

CASE 1: DRUG THERAPY OF CHRONIC STABLE ANGINA

A 55-year-old female RY, body weight 78 kg, presents to her family physician for evaluation of chest pain. She complains of occasional crushing type of chest pain and discomfort located on the left side of the chest, associated with physical exertion such as climbing stairs or lifting heavyweights. The pain does not occur at rest and is not associated with intake of meals. On examination blood pressure is 138/88 mmHg.

Medication history: **She is hypertensive for past 7 years and diabetic for 2 years. Her treatment consists of telmisartan and metformin for hypertension and diabetes respectively. There is no history of bronchial asthma.**

Personal history: **She is a smoker and an occasional drinker.**

Family history: **Father died of ischemic heart disease.**

Laboratory investigations indicate slightly abnormal lipid profile. ECG is normal.

Probable diagnosis: **Stable angina.**

Treatment Advised

- **Lifestyle modification**
- **Patient was educated to take sublingual nitroglycerin during acute attack.**
- **Tablet metoprolol succinate (beta-blocker) 50 mg orally twice a day was prescribed for prevention of angina episodes.**
- **Tab aspirin 100 mg/day**

Qa. What is ‘angina’? How would you differentiate various types of angina on the basis of their clinical presentation and pathophysiology?

Angina is not a disease, it is primarily a symptom of ischemic heart disease which occurs due to imbalance between *myocardial oxygen supply and myocardial oxygen demand*.

Angina is of three different types:

- Stable angina
- Unstable angina
- Vasospastic angina

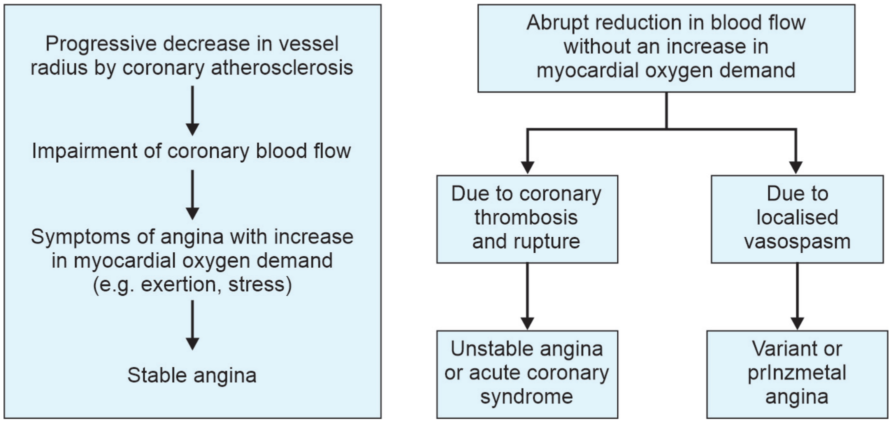

Progressive decrease in vessel radius by coronary atherosclerosis
Impairment of coronary blood flow
Symptoms of angina with increase in myocardial oxygen demand (e.g. exertion, stress)
Stable angina
Abrupt reduction in blood flow without an increase in myocardial oxygen demand
Due to coronary thrombosis and rupture
Due to localised vasospasm
Unstable angina or acute coronary syndrome
Variant or prlnzmetal angina

Fig. 4.1: Types of angina

Stable angina, also known as typical angina or angina pectoris, is characterized by chest discomfort that is provoked with exertion and alleviated at rest or with nitroglycerin. The mechanism behind stable angina is the result of supply–demand mismatch. The myocardial oxygen demand transiently exceeds the myocardial oxygen supply, which often leads to manifestations of symptoms.

Unstable angina or sometimes referred to as acute coronary syndrome, differs from stable angina in that the discomfort is usually more intense and easily provoked, and ST-segment depression or elevation on ECG may occur. With unstable angina, symptoms may occur at rest, become more frequent, severe or prolonged than the usual pattern of angina, change from the usual pattern of angina or not respond to rest or nitroglycerin.

Prinzmetal angina (vasospastic angina or variant angina) is characterized by chest discomfort or pain at rest with transient electrocardiographic changes in the ST segment, and with a prompt response to nitrates. These symptoms occur due to sudden coronary artery spasm reducing blood flow to the heart.

Qb. What are the determinants of myocardial oxygen supply and demand that can result in chest pain or angina?

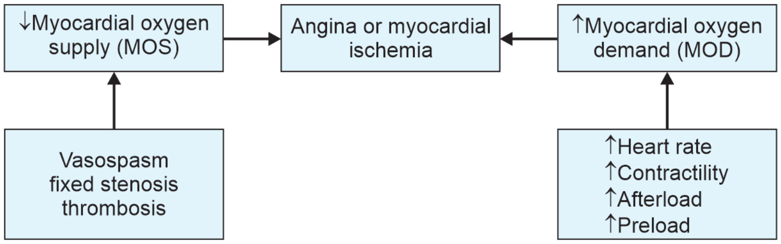

↓Myocardial oxygen supply (MOS)
Angina or myocardial ischemia
↑Myocardial oxygen demand (MOD)
Vasospasm fixed stenosis thrombosis
↑Heart rate
↑Contractility
↑Afterload
↑Preload

Fig. 4.2: Determinants of myocardial oxygen supply and myocardial oxygen demand contributing to angina

Factors which decrease myocardial oxygen supply due to reduced blood flow are:

- Focal or diffuse coronary spasm (variant angina)
- Fixed atherosclerotic narrowing of an epicardial coronary artery (stable angina)
- Rupture of an atherosclerotic plaque with platelet aggregation and thrombus formation (unstable angina or myocardial infarction)

Factors which increase myocardial oxygen demand:

- *Increase in heart rate and contractility:* Increases the workload on the heart with greater oxygen consumption and myocardial oxygen demand.
- *Increased afterload:* Resulting from increased peripheral vascular resistance leading to increased myocardial oxygen consumption and myocardial oxygen demand.
- *Increased preload:* Increases end-diastolic volume and pressure which increases diastolic ventricular wall stress. This increases end-diastolic fibre length and increased force of contraction (Frank-Starling law) and energy consumption.

Qc. Mention various formulations of nitroglycerin that are available.

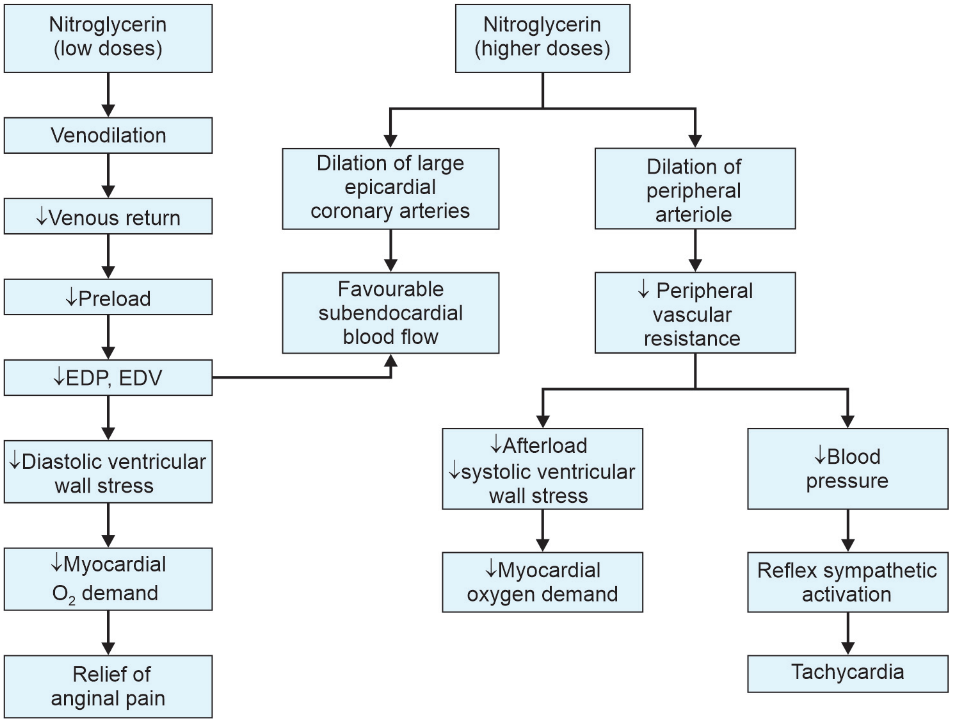
Sublingual nitroglycerin and nitroglycerin spray are referred to as shortacting preparations and used to treat acute anginal attacks.

Transdermal nitroglycerin, nitroglycerin ointment and capsules are long-acting nitrates and do not act rapidly enough to be used for acute anginal attacks. They are used to prevent episodes of angina in people who have coronary artery disease.

Qd. What are the benefits of sublingual nitroglycerin for the management of acute attack of angina?

Sublingual nitroglycerin has rapid onset of action in 1 to 2 minutes and relief of pain occurs in 5 minutes. The drug is rapidly absorbed through the oral mucus membrane, transported through the facial vein and internal jugular vein into the systemic circulation bypassing the first pass metabolism and producing immediate pain relief. Hence sublingual nitroglycerin is commonly used in the management of acute anginal pain.

Qe. How does nitroglycerin relieve anginal pain and prevent myocardial ischaemia?


Nitroglycerin (low doses)
Venodilation
↓Venous return
↓Preload
↓EDP, EDV
↓Diastolic ventricular wall stress
↓Myocardial O_2 demand
Relief of anginal pain
Nitroglycerin (higher doses)
Dilation of large epicardial coronary arteries
Favourable subendocardial blood flow
Dilation of peripheral arteriole
↓ Peripheral vascular resistance
↓Afterload ↓systolic ventricular wall stress
↓Myocardial oxygen demand
↓Blood pressure
Reflex sympathetic activation
Tachycardia

EDV: End diastolic volume; EDP: End diastolic pressure

Fig. 4.3: Effects of nitroglycerin use in the management of ischaemic heart disease

Decrease in myocardial oxygen demand is the key mechanism through which nitroglycerin (NTG) relieves anginal pain rather than increase in myocardial oxygen supply. At low doses, nitrates preferentially dilate the veins, increasing the venous capacitance and causing venous pooling. This decreases preload, diastolic ventricular wall stress and myocardial oxygen demand. At higher doses, it decreases peripheral arteriolar resistance which reduces afterload and systolic ventricular stress.

Nitroglycerin improves subendocardial perfusion due to reduction in diastolic ventricular wall stress which helps to increase the blood flow through the subendocardial blood vessels during diastole and thus reduces subendocardial crunch.

Nitroglycerin selectively dilates large epicardial coronary arteries (> 200 µm) without altering the tone of small to medium arterioles (resistance vessels). This increases the blood flow in the coronary arteries distal to the narrowing and in the collateral blood vessels and further facilitates the blood flow to the ischaemic subendocardium through the autoregulatory mechanism.

Antiplatelet effect of nitroglycerin due to increased cGMP in the platelet, improves blood flow to the ischaemic regions due to inhibition of platelet aggregation.

Qf. During an acute attack of angina, if 3 to 5 tabs of nitroglycerin fails to provide pain relief and the patient takes high doses of nitroglycerin, will it produce beneficial action? Explain with reasons.

Nitroglycerin has a rapid onset of action and pain relief is achieved immediately. If 3 tabs of nitroglycerin 0.5 mg each over a 15 minute period do not relieve anginal pain it may be myocardial infarction or unstable angina or other causes of pain. The patient should be transported to the emergency department of the hospital for further evaluation of chest pain.

High doses of nitrates do not produce much beneficial action. At high doses, there is more venous pooling and pronounced decrease in systemic vascular resistance causing marked reduction in cardiac output and blood pressure. Severe hypotension can produce large decrease in coronary perfusion leading to aggravation of angina and producing symptoms of fatigue, weakness and dizziness.

Due to significant fall in blood pressure, there is increased activation of sympathetic reflexes increasing the adrenergic tone and tachycardia. This offsets the decrease in preload and afterload actions of nitroglycerin and overrides the beneficial actions of nitroglycerin and can aggravate ischaemia.

Qg. What is the danger associated with the use of nitrates in a patient with coexisting autonomic dysfunction?

At normal therapeutic doses of nitrates, fall in blood pressure is compensated by activation of sympathetic system which helps to normalise the blood pressure.

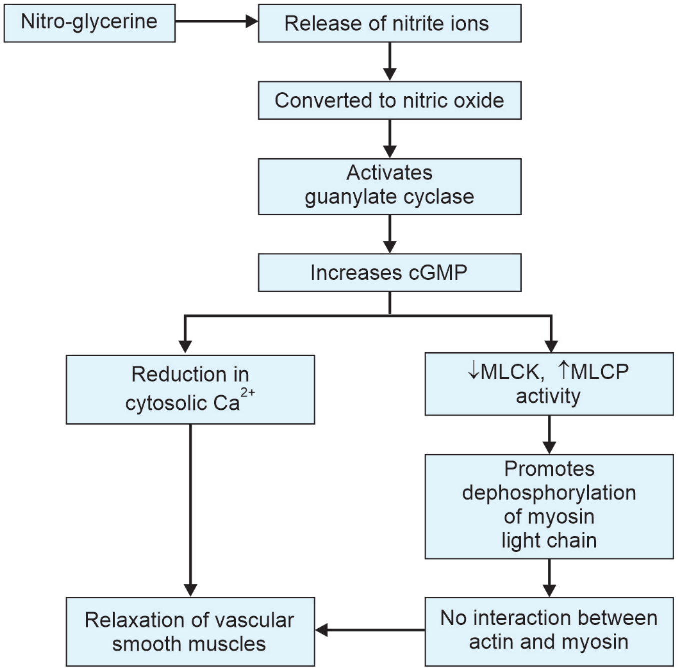
In patients with autonomic dysfunction there is inability to increase sympathetic outflow and hence fall in blood pressure cannot be compensated. This can lead to life-threatening hypotension and even aggravation of ischaemia.

Qh. How does nitroglycerin act to dilate the blood vessels?

Nitroglycerin is denitrated by mitochondrial aldehyde dehydrogenase (mALDH) in smooth muscle and other cells. This results in the release of nitrite ion, which is then converted to nitric oxide. Nitric oxide that is released stimulates guanylate cyclase in smooth muscle, producing an increase in cGMP which causes vasodilation.

Relaxation in vascular smooth muscle is due to

- Reduction in cytosolic calcium
- Dephosphorylation of myosin light chain caused by increased myosin light chain phosphatase and decreased myosin light chain kinase activity. The resultant effect is reduced interaction between actin and myosin.


Nitro-glycerine
Release of nitrite ions
Converted to nitric oxide
Activates guanylate cyclase
Increases cGMP
Reduction in cytosolic Ca^{2+}
↓MLCK, ↑MLCP activity
Promotes dephosphorylation of myosin light chain
No interaction between actin and myosin
Relaxation of vascular smooth muscles

MLCK: Myosin light chain kinase; MLCP: Myosin light chain phosphatase

Fig. 4.4: Mechanism of action of nitroglycerin

Qi. Given that dipyridamole is a vasodilator with antiplatelet properties, why is it not used in ischemic heart disease? Explain by comparing the haemodynamic effects of dipyridamole with nitroglycerin.

The subendocardial layer of myocardium is most vulnerable to ischaemia. In response to hypoxia, the arterioles in the ischemic cardiac tissue are dilated to maintain blood flow to the ischemic tissues. Oral nitrates can only *dilate large epicardial coronary artery with diameter (> 200 µm) without any effect on coronary resistance vessels, that is, small arterioles.* This facilitates blood flow distal to the stenosis of the coronary artery, opens up the collaterals and *augments the blood flow to the ischemic areas, through the arterioles which are maximally dilated due to hypoxia*. Thus, nitrates have beneficial action in myocardial ischaemia.

Dipyridamole in contrast to the actions of oral nitrates is a non-selective vasodilator. In addition to the large coronary vessels, it also dilates the smaller arterioles. Due to dilatation of arterioles in the surrounding healthy heart tissue, the *blood from the ischemic regions is diverted to the healthy tissue and this is known as coronary steal phenomenon.* Thus, the blood supply to the ischemic myocardium is impaired, further worsening the condition.

Qj. What are the options for chronic prevention of anginal episodes?

Medicines which are commonly used for the prevention of anginal attacks are beta-blockers, calcium channel blockers (CCBs), long-acting nitrates and ranolazine.

Qk. Justify the selection of metoprolol succinate, a beta-blocker in case of RY, for prophylaxis of acute attack of angina.

As per the current guidelines all patients with stable angina should receive beta-blocker as initial therapy unless contraindicated.

The benefits of beta-blockers are as follows:

- Beta-blockers inhibit sympathetic stimulation of the heart, reducing heart rate and contractility; this can decrease myocardial oxygen demand and thus prevent and relieve angina in patients with coronary artery disease (CAD).
- Since beta-blockers reduce the heart rate-blood pressure product during exercise, the onset of angina or the ischaemic threshold during exercise is delayed or avoided.
- Beta-blockers are generally considered the most effective agents at preventing silent myocardial ischaemia.
- Beta-blockers lower morbidity and mortality in patients with coronary artery disease and heart failure.

Considering the above mentioned benefits of beta-blockers, and given that RY has no history of reactive airway disease or peripheral arterial disease during the clinical presentation, beta-blocker appears to be the best option for RY.

Ql. Mention the mechanisms through which beta-blockers relieve angina pain.

Beta-blockers reduce the frequency and severity of angina attacks and increase exercise tolerance by doing one or both of the followings:

- Decreasing myocardial oxygen demand by reducing heart rate, myocardial contractility and blood pressure.
- Enhances blood flow to the subendocardial regions by increasing the diastolic perfusion time.

Qm. What is the role of beta-blockers in the treatment of unstable angina?

Beta-blockers when used in unstable angina have shown to decrease ischaemic symptoms and in the occurrence of myocardial infarctions. They are indicated in select patients with tachycardia or hypertension with ongoing chest pain. In haemodynamically compromised patients, beta-blockers have been demonstrated to increase the risk of potential complications of cardiogenic shock and heart failure. Therefore, clinical judgement should be used prior to prescribing beta-blockers, in patients with unstable angina.

Qn. Beta-blockers are not used in the treatment of variant angina. Explain with reasons.

Variant angina, vasospastic angina or prinzmetal angina is caused by diffuse or segmental spasm in the coronary arteries. There is decrease in blood supply to the myocardium generating symptoms like chest pain. The use of beta-blockers, especially those with non-selective adrenoceptor blocking effects, should be avoided, because these drugs can aggravate the symptoms, by blocking $\beta 2$-receptors that produce vasodilator effects, leaving α mediated vasoconstriction effect unopposed. Predominant α-mediated constriction of blood vessels further reduces coronary blood flow leading to exaggeration of chest pain.

Qo. If RY has coexisting bronchial asthma or peripheral arterial disease, would the decision to initiate therapy with beta-blocker change? Explain.

Although beta-blockers are considered as the first line treatment in chronic prevention of angina, they are not preferred in patients of ischaemic heart disease with coexisting bronchial asthma or peripheral arterial disease because of the following reasons:

- The antagonistic action of beta-blockers on β_2-receptors of the bronchial smooth muscle may precipitate acute bronchospasm and cause severe asthma exacerbations particularly at high doses.

- In peripheral circulatory disorders such as Raynaud's disease, frost bite, beta-blockers would block β_2-receptors of the smooth muscle of blood vessels. This results in unopposed α1–receptor mediated vasoconstriction, further aggravating the existing vasospasm in the coronary artery with precipitation of angina.

Cardioselective beta-blockers with relatively less effect on β2-receptors of bronchial smooth muscle or peripheral blood vessels are likely to be safe and tolerable. However, physicians may prefer next best alternative option to beta-blockers in order to avoid adverse consequences and also the cardioselectivity is not absolute, it is only relative.

Qp. If the physician wishes to switch drug therapy due to intolerance with beta-blocker, would calcium channel blocker be the right option in case of RY? Explain with reasons.

If beta-blocker is intolerable or is risky as in reactive airway disease or peripheral vascular disease, therapy with heart rate limiting calcium channel blocker is the next best option provided there is adequate heart rate to tolerate therapy. If the blood pressure of the patient is elevated, calcium channel blocker is the best alternative to beta-blocker.

In patients who have low heart rate and marginal blood pressure, *ranolazine* may be considered. *Long-acting nitrates are typically reserved for add-on therapy*. In case of patient RY, blood pressure is preserved and heart rate is normal and hence calcium channel blocker may be preferred for the management of ischemic heart disease with underlying conditions of bronchial asthma or peripheral arterial disease.

Qq. Enlist the calcium channel blockers that are useful in the treatment of angina. How do the calcium channel blockers produce beneficial effect in chronic stable angina?

The calcium channel blockers (CCBs) used in the treatment of angina are divided into two groups:

- **Dihydropyridines:** Nifedipine, amlopidine, felodipine, nicardipine
- **Non-dihydropyridines:** Verapamil and diltiazem

All calcium channel blockers relieve anginal pain by increasing the myocardial oxygen supply and decreasing the myocardial oxygen demand. This occurs due to the effect of calcium channel blockers on coronary and peripheral blood vessels. The vasodilatory effects of CCBs in the coronary circulation increase myocardial oxygen supply, whereas dilation of the peripheral arterioles leads to a reduction in afterload and subsequently myocardial oxygen demand.

Qr. In a patient with low left ventricular ejection fraction, should verapamil be used as an antianginal agent? Explain with reasons.

In *patients with angina and heart failure*, intravenous verapamil causes a marked decrease in contractility and also in left ventricular function due to negative inotropic and chronotropic effect on the heart. Verapamil reduces the magnitude of Ca^{2+} current and delays the recovery of slow Ca^{2+} channels. This accounts for its negative inotropic and chronotropic effect of verapamil.

In *angina without heart failure*, verapamil acts by decreasing the peripheral vascular resistance, reduces afterload and improves ventricular performance. The reflex increase in adrenergic tone resulting from fall in blood pressure is offset by direct cardiodepressant effect. Thus, there is no tachycardia. These effects are favourable in the management of angina in the absence of heart failure.

(Note: Verapamil depresses the rate of sinus node pacemaker and slows AV conduction. This is the basis of its use in supraventricular arrhythmias.)

Qs. Explain why amlodipine or nicardipine is preferred over nifedipine in the management of angina.

Dihydropyridines such as nifedipine are predominant arterial vasodilators with a little or no effect on cardiac tissue. Nifedipine has a rapid onset of action, causing a sudden fall in blood pressure with activation of reflex sympathetic baroreceptor reflexes causing tachycardia, which is undesirable in the treatment of angina.

Amlodipine has long plasma half-life, maintains a steady plasma concentration and hence there is less tachycardia than nifedipine.

Nicardipine has selectivity for coronary blood vessels. They preferentially dilate the coronary blood vessels, increasing the coronary blood flow and myocardial oxygen supply. This action is beneficial for the treatment of angina.

Therefore, amlodipine or nicardipine is preferred over nifedipine in the management of angina.

Case Continued

RY responded well to treatment and her symptoms improved. After 4 months she abruptly stopped taking her prescribed tablet metoprolol, as she forgot to get her prescription refilled. Two days later, she suffered from an anginal attack, which was unresponsive to 3 tabs of nitroglycerine and admitted to the hospital and treated.

Qa. What could be the possible reason for precipitation of anginal attack? Could this episode have been prevented? If yes, what precautions need to be taken to prevent such future attacks?

This could possibly be a case of beta-blocker withdrawal syndrome, which is a rebound phenomenon due to abrupt discontinuation of treatment.

Long-term treatment with beta-blocker causes upregulation or supersensitivity of β-receptors due to β-blockade. This can cause an exaggerated response of the β-receptors to the circulating catecholamines, resulting in increased sympathetic activity and myocardial oxygen demand placing the patient at risk for cardiovascular events.

Abrupt discontinuation of β-blockers should be discouraged. If beta-blockers are to be discontinued there should be gradual tapering of dose over a period of 1–2 weeks. The patient should be carefully monitored during the period of taper and should seek medical attention if symptoms of angina appear. The patient should be warned about the adverse consequences of abrupt discontinuation of beta-blocker and advised not to withdraw beta-blocker treatment suddenly.

Case Continued

The patient RY recovered and was discharged. Following discharge she was able to do her routine activities but was bothered by occasional episodes of chest pain associated with exertion and physical activity. The chest pain subsides with rest or NTG. The quality and location of pain is unchanged. The blood pressure and heart rate is normal. On consultation, RY's cardiologist prescribes isosorbide mononitrate in addition to beta-blocker metoprolol which she was taking earlier.

Qa. What is the rationale for combining isosorbide mononitrate with beta-blocker in the management of angina as in case of RY?

The following benefits are obtained by combining isosorbide mononitrate with beta-blocker:

1. The undesirable effect of one drug is counterbalanced by the other drug in combination. Nitrate-induced tachycardia in response to the fall in blood pressure can be offset by the action of beta-blocker which decreases the heart rate and contractility.

   Nitrates increase venous capacitance and attenuate the increase in left ventricular end diastolic volume associated with beta blockade. Nitrates also alleviate increase in coronary vascular resistance associated with beta blockade.
2. Additive or synergistic effect is achieved by combining nitrates with beta-blocker. Both beta-blockers and nitrates relieve symptoms of angina mainly by decreasing the myocardial oxygen demand and favour redistribution of blood flow to the subendocardial regions and hence additive or synergistic effect is observed.

Qb. Does sublingual NTG lead to the development of tolerance? How does dosage and frequency of use of oral nitrates relate to the development of tolerance?

Shortacting formulations such as sublingual nitroglycerin have a rapid onset of action and short duration of effect. They are used intermittently at the time of anginal attack and prior to exercise or stress and are not likely to induce tolerance.

Frequently repeated or continuous use of high doses of oral nitrates (isosorbide dinitrate, isosorbide mononitrate) lead to the development of tolerance.

Qc. What are the underlying mechanisms for the development of tolerance?

The underlying mechanisms for the development of tolerance can be categorized as:

True vascular tolerance which is due to reduced capacity of vascular smooth muscle to convert nitroglycerin to nitric oxide.

Pseudotolerance due to mechanisms extraneous to vessel wall and are as follows:

- Increased neurohumoral activation resulting in increased production of catecholamines and activation of renin–angiotensin–aldosterone system.
- Increased plasma volume expansion
- Cellular depletion of sulfhydryl groups
- Generation of free radicals

Qd. What are the measures to limit the development of tolerance that is likely to develop with long-acting oral nitrates?

The following measures should be undertaken to prevent the development of tolerance or restore responsiveness:

1. Intermittent treatment with oral nitrates with a nitrate free interval of at least 8 hours needs to be maintained to avoid the development of tolerance.
2. The nitrate free interval can be arranged during the night when physical activity and exertion is minimum. But in patients with nocturnal or early morning angina nitrate free interval period can be arranged during the day.
3. During the nitrate free period rebound angina can be a problem hence another class of anti-anginal agent can be used as in case of RY, metoprolol therapy will provide continuous protection even during the nitrate free interval.
4. Avoid using high doses of organic nitrates. It is recommended to start initially with low dosages and titrate upwards as needed.
5. Avoid continuous IV infusion of nitroglycerin. The night dosing can be omitted in exertional angina.

Qe. What is the danger of prescribing nitrates with sildenafil?

Sildenafil is used in the treatment of erectile dysfunction and pulmonary artery hypertension. It acts by inhibiting phosphodiesterase (PDE5), an enzyme responsible for the degradation of cGMP and increases cGMP concentration responsible for vasodilation. Nitrates when coadministered with sildenafil, act synergistically to cause profound increase in cGMP which leads to excess vasodilation and reduction in blood pressure drastically by more than 25 mmHg. The patient should be warned to avoid taking sildenafil if he is on treatment with nitrates.

Qf. Occupational exposure to nitroglycerin commonly used in industrial explosives leads to the development of special type of tolerance and is termed Monday's disease. Explain.

Workers of nitroglycerin explosives manufacturing industry experience severe headache, nausea, dizziness and flushing in the head and neck initially after joining work. These symptoms are manifestations of the haemodynamic effects of nitrates. The symptoms gradually disappear as the days progress. This is due to the development of tolerance resulting from repeated exposure to nitrates for prolonged period. After a gap of few days remaining away from work, when they return back to work the symptoms reappear. This is termed 'Monday disease'. An interval of few days acts as the nitrate-free interval which restores the responsiveness to nitrate leading to reappearance of the same symptoms.

Qg. Mention the newer antianginal agents. Discuss their benefits and side effects of their use in the management of angina.

Ranolazine

Ranolazine is a second line antianginal agent without haemodynamic effect. It is useful in chronic angina and not in acute angina. It preferentially *inhibits late* Na^+ *channels* which are usually increased in ischaemia. Activation of these channels leads to myocardial Ca^{2+} overload resulting in more cardiac work. It has also weak β-blocking activity.

The disadvantage is that it is metabolized by CYP 3A4 and 2D6 and therefore potential for drug–drug interactions may lead to poor health outcomes.

Ivabradine

Ivabradine was approved for symptomatic management of stable angina pectoris. It *reduces the automaticity of SA node by inhibiting HCN channels and decreasing the funny current.* It decreases the heart rate, thereby reducing the myocardial oxygen demand and exerting antianginal effect. It is important to note that it has only *negative chronotropic effect but no negative inotropic effect* which means it reduces heart rate but does not affect contractility.

Ivabradine, if coadministered with verapamil, diltiazem or beta bocker may cause bradycardia and AV block.

It is thought to induce phosphenes by blocking hyperpolarization-activated and cyclic nucleotide gated (HCN) in photoreceptors. There is enhanced lightness in restricted areas of visual field. Atrial fibrillation and QT prolongation also can occur.

Nicorandil

Nicorandil has been recommended as one of the second line treatments for chronic stable angina. It acts as a *potassium channel opener that relaxes vascular smooth muscle through membrane hyperpolarization* via increased transmembrane potassium conductance and through increased concentration of cyclic GMP. It is shown to dilate normal and stenotic coronary arteries and reduces both ventricular preload and afterload. It confers survival benefit in patients with ischaemia. Unlike nitrates, the long-term use of *nicorandil does not appear to cause significant drug tolerance or rebound angina*.

The most common side effect of nicorandil is headache which is due to vasodilation. Gastrointestinal side effects are also common. Nicorandil can cause serious skin, mucosal and eye ulcerations including gastrointestinal ulcers which may progress to perforation.

Trimetazidine

Trimetazidine is a second line drug in stable angina without hemodynamic effect. It *inhibits free fatty acid (FFA) β-oxidation pathway*, thereby shifting the cardiac metabolic pattern from fatty acid to glucose pathway which produces less ATP and requires less oxygen so decreases myocardial oxygen demand. This is particularly useful in patients with coexisting diabetes mellitus and is known to improve left ventricular function in diabetic patients with coronary artery disease.

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Chapter
5

Antithrombotic Therapy and Drugs for Myocardial Infarction

CASE 1: USE OF UNFRACTIONATED HEPARIN AS PROPHYLAXIS OF VENOUS THROMBOSIS PRIOR TO SURGERY

LM, a 70-year-old female, weight 85 kg, undergoes major surgery for pancreatic cancer. Medical history suggests 25 years history of diabetes and 30 years history of hypertension with stage 2 kidney disease.

Low-dose unfractionated heparin (LDUFH), administered as 5,000 units SC every 8 to 12 hours to prevent the risk of vein thrombosis and pulmonary embolism.

Qa. Mention the steps involved in the pathogenesis of venous thrombosis.

Thrombosis is a pathological condition resulting from inappropriate activation of haemostatic mechanisms. Virchow's triad proposed in 1856 explains the mechanisms and pathogenesis of venous thrombosis. The triad consists of:

1. Changes in the vessel wall
2. Abnormalities of blood flow
3. Alteration in blood coagulability

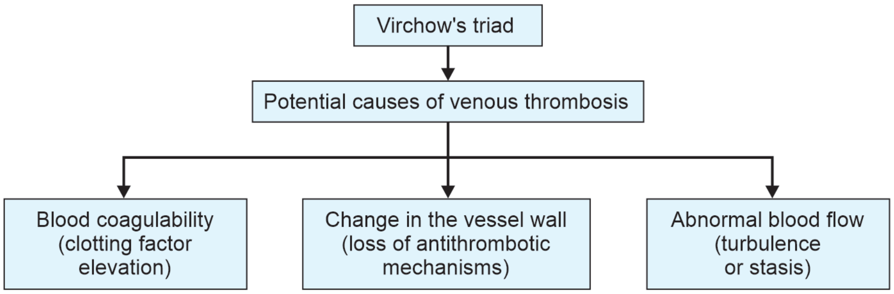

Virchow's triad
Potential causes of venous thrombosis
Blood coagulability (clotting factor elevation)
Change in the vessel wall (loss of antithrombotic mechanisms)
Abnormal blood flow (turbulence or stasis)

Fig. 5.1: Development of venous thrombosis

Qb. What is the aim of anticoagulant therapy?

Anticoagulant drug therapy is aimed at preventing pathologic clot formation in patients at risk and at preventing clot extension and/or embolization in patients who have experienced thrombosis.

Qc. Illustrate the coagulation pathway and enlist the drugs used for anticoagulation.

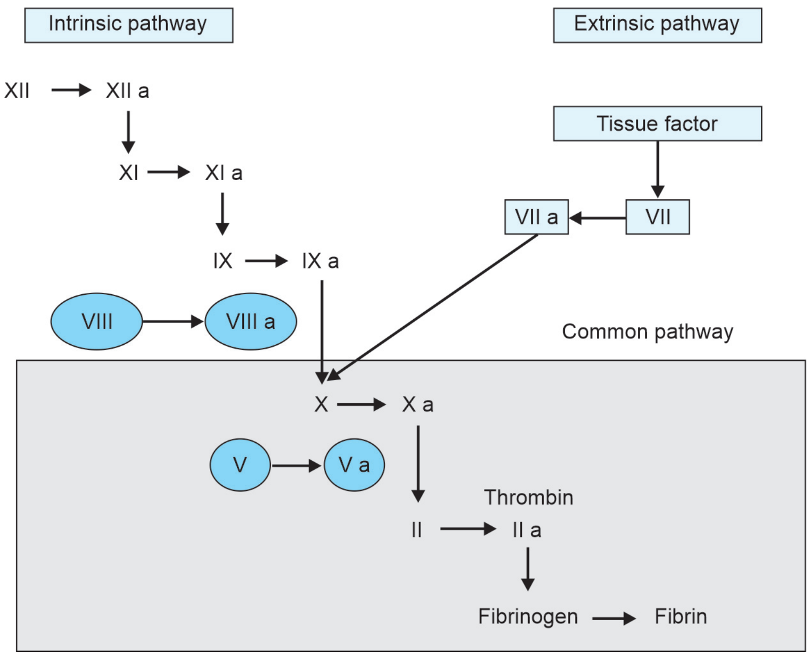

Intrinsic pathway
Extrinsic pathway
XII
XII a
Tissue factor
XI
XI a
VII a
VII
IX
IX a
VIII
VIII a
Common pathway
X
X a
V
V a
Thrombin
II
II a
Fibrinogen
Fibrin

Fig. 5.2: Coagulation pathway

Steps of the coagulation cascade that result in clot formation are the following:

- Endothelial damage leads to the activation of extrinsic and intrinsic pathways involved in clot formation.
- Activation of extrinsic pathway releases VIIa which directly activates the common pathway via factor X.
- Intrinsic pathway initiated by XIIa and through a chain of events lead to the conversion of X to Xa.
- The activated form of factor X mediates the conversion of prothrombin to thrombin which results in the final step of conversion of fibrinogen to fibrin and clot formation.

Anticoagulants may be classified as under:

Parenteral anticoagulants

a. Heparin
b. Low-molecular-weight heparin, e.g. enoxaparin, dalteparin, tinzaparin, and nadroparin
c. Synthetic heparin derivatives: Fondaparinux
d. Thrombin inhibitors: Lepirudin, bivalirudin, argatroban, and danaparoid

Oral anticoagulants

a. Coumarin derivatives: Warfarin, acenocumarol
b. Newer oral anticoagulants: Dabigatran, rivaroxiban, and apixaban

Qd. How does heparin facilitate the actions of antithrombin III, and play a role in the prevention and treatment of venous thrombosis?

Antithrombin III inactivates thrombin and other coagulation factors (XIIa, XIa, XIa, Xa) where 'a' denotes activated factor. Inactivation of clotting factors prevents their further participation in the coagulation cascade preventing pathological clot formation.

Heparin accelerates the binding reaction between antithrombin III and clotting factors by 1000 fold specially against IIa and Xa so that the reaction occurs at a faster rate producing the desired therapeutic effect. Otherwise, the reaction between antithrombin III and clotting factors is very slow.

Actions of heparin on antithrombin III mediated inactivation of clotting factors

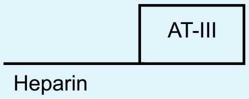
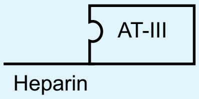
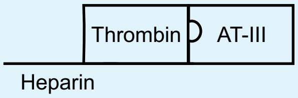
Step 1		Binding of negatively charged heparin molecule to positive charge on antithrombin III
Step 2		Conformational change in antithrombin III increasing its receptiveness to the coagulation factors
Step 3		Catalytic surface of heparin facilitates reactivity between antithrombin III and thrombin

Fig. 5.3: Mechanism of action of heparin

Of Note: Thrombin inactivation requires binding surface on heparin for enhanced catalytic reactivity between antithrombin III and thrombin, whereas inactivation of Xa does not require binding to the catalytic surface of heparin.

Qe. How does molecular weight or structure of heparin determine differential anticoagulant action especially on IIa and Xa?

Heparin molecule uses highly negative pentasaccharide structure to bind to antithrombin which is positively charged and induces conformational change required for conjugation reaction.

Molecular weight and length of heparin molecule controls the conjugation reaction between antithrombin III and the clotting factor.

Heparin (molecular weight or structure)	*Effect on Xa*	*Effect on thrombin (IIa)*
Unfractionated heparin: Molecular weight ranges 1–30 kDa (Av 20 kDa) Contains more than 18 monosaccharide units	Inactivation of Xa	Complete inactivation of thrombin
Low molecular weight heparin (LMWH) Molecular weight is 3–4 kDa Shorter in length, contains less than 18 monosaccharide units	Inactivation of Xa	Lesser action on thrombin
Synthetic heparin derivative (fondaparinux) Pentasaccharide structure	Inactivation of Xa	No effect on thrombin

***Effect on thrombin*:** To catalyze most efficiently the inactivation of thrombin by antithrombin III, simultaneous binding of both thrombin and antithrombin III is required for subsequent conjugation reaction and inactivation of thrombin.

Unfractionated heparin is lengthy (>18 monosaccharide units) and allows simultaneous binding of thrombin and antithrombin III resulting in antithrombin-induced inactivation of thrombin.

Low molecular weight heparin (LMWH) is of shorter length (lesser than 18 monosaccharide units) and binds poorly to thrombin and hence has lesser action on thrombin.

Fondaparinux, a synthetic heparin, is a pentasaccharide structure which is of sufficient length to bind to antithrombin III only and does not offer catalytic surface for binding of thrombin and therefore has no effect on thrombin.

Effect on Xa: Inactivation of Xa requires binding of heparin to antithrombin III only and inducing conformational change in antithrombin III. Although fondaparinux is a pentasaccharide structure and does not provide catalytic surface for Xa to bind, it induces conformational change in antithrombin III-heparin complex rendering it susceptible to react with Xa leading to its inactivation. Unfractionated heparin, low molecular weight heparin and synthetic heparin derivatives inactivate factor Xa.

Qf. What is the rationale for initiating prophylaxis with low-dose unfractionated heparin (LDUFH) subcutaneously in LM prior to surgery?

LM, a 70-year-old female, is at high risk for deep vein thrombosis and pulmonary embolism, because of postoperative immobilization, old age and obesity. For critically ill, postoperative patients with comorbidities (diabetes, hypertension and kidney disease) requiring parenteral venous thromboembolism prophylaxis, *unfractionated heparin (UFH) in low doses* is the best therapeutic option. This is because at low doses, unfractionated heparin is cleared through the reticuloendothelial system by rapid, zero order process but at high doses this system saturates and further elimination occurs renally. As clearance becomes dependant on the kidney, increased or prolonged UFH dosing especially in patients with renal dysfunction leads to a disproportionate increase in intensity and duration of the anticoagulant effect with increased risk of haemorrhage.

Administering the drug subcutaneously, at low dose, will prevent rapid rise in plasma concentration and reduce the risk of toxicity. Furthermore, UFH has a short half-life, its action can be reversed with protamine sulphate and the effect can be rapidly terminated. Hence, prophylactic therapy with low dose of unfractionated heparin (UFH) is used prior to surgery in case of LM.

Qg. Considering that LM is a patient of kidney disease, do you think low molecular weight heparins (LMWH) and fondaparinux are suitable alternatives to unfractionated heparin (UFH)? Explain with reasons.

Low molecular weight heparins and fondaparinux are mainly eliminated by renal excretion. In cases of chronic renal insufficiency there is accumulation of LMWH and fondaparinux with subsequent prolongation of half-life. Due to the risk of accumulation and increased bleeding, patients with *fluctuating renal function or with a creatinine clearance less than 30 ml/min are not candidates for LMWH or fondaparinux. Dalteparin*, however, has shown minimal tendency to accumulate in patients with chronic kidney disease and may be safe to use in this patient population.

Case Continued

On day 2, the CBC report showed a drop in platelet count from 2,50,000/µl to 1,95,000/µl. Heparin therapy was continued and platelet count was monitored on a regular basis.

Qa. What could be the reason for the drop in platelet count and for the decision to continue therapy with heparin in case of SK?

The decrease in platelet count is possibly due to heparin-induced thrombocytopenia (HIT). There are two forms of HIT. In type 1 HIT, thrombocytopenia is mild and occurs during the first 48 to 72 hours after the initiation of heparin therapy. There is no immunologic basis for type 1 HIT and is due to the direct effect of heparin on platelet function causing transient platelet aggregation and consumption and reduction in platelets from the circulation.

The platelet count rarely drops below $100 \times 10^3/\mu l$ and may normalize without discontinuation of heparin. Hence heparin therapy was continued.

CASE 2: HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

A 36-year-old lady RY, got up in the morning with leg swelling up to thigh. She was on hormones for polycystic ovarian disease (PCOD). Leg was swollen and tense and there was some pain and discomfort while walking. She denied symptoms of cough, dyspnea and chest pain.

Duplex USG is positive for DVT up to the femoral veins and iliac vein is clear.

Treatment was initiated with loading dose of unfractionated heparin followed by IV infusion.

Qa. Explain the rationale for administering loading dose of unfractionated heparin followed by IV infusion, in the management of acute DVT or pulmonary embolism.

In an acute setting of deep vein thrombosis (DVT) or pulmonary embolism (PE) the coagulation cascade is active and to neutralise high concentration of clotting factors, large dose of heparin is required. Therefore, treatment is initiated with a loading dose of heparin so that plasma therapeutic concentration is achieved rapidly and immediate therapeutic effect is produced.

To maintain the therapeutic effect, heparin is administered by IV infusion because heparin has short half-life and the titration is based on activated partial thromboplastin time (aPTT). Initial heparin loading doses of 60 to 100 units/kg followed by an infusion rate of 13 to 25 units/kg/hour are commonly recommended.

Qb. Can subcutaneous or intramuscular routes be used as alternatives to IV administration of heparin?

Heparin can be administered via subcutaneous route, but the absorption of the drug into the systemic circulation is slow and bioavailability is less compared to intravenous route. Intramuscular route is avoided because of the potential for haematoma formation with heparin.

Case Continued

Eight days after the start of therapy with UFH, platelet count decreased drastically to 80,000/µl from 2,15,000/µl and the anti-platelet factor 4-heparin complex antibody was strongly positive. He was diagnosed with heparin-induced thrombocytopenia (HIT) with thrombosis. Heparin was stopped immediately and argatroban was initiated intravenously as a replacement anticoagulant.

Qa. Explain the underlying reason for drastic reduction in platelet count, following administration of UFH in patient RY.

A *50% reduction in platelet count* from the baseline that is usually below $100 \times 10^3/\mu l$ or formation of new thrombus during anticoagulant therapy may be indicative of type 2 heparin-induced thrombocytopenia (HIT). It has a delayed onset, *develops 5–15 days after the start of heparin therapy*. This is a severe form of HIT and is a result of *immune mediated response characterized by the generation of IgG antibodies against heparin–platelet factor IV (PF4) complex*. Binding of antibodies to heparin–PF4 complex on the surface of the platelets results in activation of platelets and release of procoagulant material into the circulation which in turn promote excessive thrombin generation leading to thrombosis in the arterial and venous systems. Thrombocytopenia is due to antibody mediated removal of platelets from the circulation.

Qb. Is platelet transfusion indicated for HIT? What is the rationale for substituting heparin with an alternative non-heparin anticoagulant?

Heparin-induced thrombocytopenia (HIT) is strongly associated with thrombosis. Despite thrombocytopenia, bleeding is rare. Platelet transfusions should be avoided as they may increase the thrombogenic effect.

Since the patients with HIT are at *high risk for thrombotic events*, they should be treated with alternative non-heparin anticoagulant, typically a direct thrombin inhibitor such as danaparoid, argatroban or bivalirudin, and may be routinely monitored with the activated partial thromboplastin time (aPTT).

Qc. Can low molecular weight heparin (LMWH) or warfarin be used as replacement anticoagulants for unfractionated heparin (UFH) in HIT? If not, mention the alternative anticoagulants which can be instituted in the treatment of RY.

Low molecular weight heparin is less likely to cause formation of antibody to heparin–PF4 complex than unfractionated heparin but will always cross react with antibodies formed against unfractionated heparin–PF4 complex and cannot be used to treat patients with HIT. If positive antibodies have been detected, *LMWH cannot be used due to cross reactivity between glycosaminoglycans and warfarin therapy may exacerbate thrombosis in the patient with ongoing HIT*.

Patients with heparin-induced thrombocytopenia are at high risk for thrombotic events and should be treated with alternative anticoagulants, typically a *direct thrombin inhibitor, Argatroban* is approved in the prophylaxis and treatment of patients with HIT. *Bivalirudin* can also be safely used in critically ill and HIT patients.

Several *novel oral anticoagulants exist, e.g. rivaroxaban, dabigatran and apixaban* may be beneficial for HIT, particularly in cases refractory to standard therapies.

CASE 3: USE OF LOW MOLECULAR WEIGHT HEPARIN (LMWH) IN OUTPATIENT SETTING

A 25-year-old male patient 'ST' with complaints of cramping pain in the right leg in the calf with swelling and redness observed behind the knee. A duplex ultrasound is positive for DVT and immediate anticoagulation is indicated. The patient refuses hospitalisation and wishes to be treated at home. ST was prescribed enoxaparin (1.5 mg/kg sc daily) and was advised regular follow-up visits for transition to warfarin.

Qa. Mention the advantages of use of low molecular weight heparin in outpatient treatment setting of deep vein thrombosis.

- LMWH can be self-administered at home via subcutaneous injection reducing or eliminating hospital stays.

- LMWH exhibits improved bioavailability after subcutaneous injection explained by its reduced binding affinity for plasma proteins and endothelial cells.
- It has a longer pharmacodynamic effect and predictable dose response compared to UFH. It is administered every 12 to 24 hours at fixed doses.
- No regular blood monitoring of activated partial thromboplastin time (aPTT) is required.
- There is reduced likelihood of side effects such as bleeding and heparin-induced thrombocytopenia.

Qb. What precautions have to be considered while prescribing enoxaparin on an outpatient basis?

The drug is cleared through kidney, therefore, avoided in renal insufficiency. Long half-life and lack of specific antidote warrants exercising caution.

CASE 4: BLEEDING FROM HEPARIN THERAPY

An 83-year-old female LK, is admitted for shortness of breath. She is frail, weighing only 40 kg. Routine investigations reveal haemoglobin of 12.5, creatinine of 1.3, and she is found to have deep venous thrombosis of her right lower extremity. A perfusion scan of her lungs is consistent with a pulmonary embolism. She is started on low molecular weight heparin and other supportive measures. She improves, but on the third day of treatment, develops severe hematuria and gastrointestinal bleeding; her haemoglobin falls to 8.6.

Qa. Explain the reason for the occurrence of hematuria and gastrointestinal bleeding in LK following heparin therapy. How could this adverse reaction been prevented?

Use of low molecular weight heparin (LMWH) in patients with renal failure particularly in elderly and frail patients, can cause haemorrhage and should not be used.

It is recommended that unfractionated heparin (UFH) be used to provide full anticoagulation therapy in patients with severe renal insufficiency. If LMWH is chosen, monitoring should be performed with therapeutic anti-factor Xa activity.

LMWH is excreted entirely by the kidneys and should not be used in patients with compromised renal function. UFH, however, is rapidly metabolized by a saturable, zero-order mechanism, mainly by the reticuloendothelial system. Metabolism is followed by a slower first-order renal clearance. Less than 10% is excreted unchanged in urine. The *short half life, easy reversibility with protamine sulphate, non-renal clearance and the familiarity of clinicians with the drug* makes UFH the anticoagulant of choice in patients with renal failure and for patients with high risk of bleeding.

Qb. What are the coagulation parameters that need to be estimated for monitoring therapy with various anticoagulants?

Various anticoagulants are monitored using the following parameters:

- Unfractionated heparin (UFH), lepirudin and argatroban require dose adjustment according to the therapeutic range of the *activated partial thromboplastin time (aPTT).*

- Low molecular weight heparin (LMWH), fondaparinux and danaparoid have to be controlled by their *antifactor Xa* activity in renal impairment.
- Vitamin K antagonists or warfarin administration necessitate dose adjustment based on *prothrombin time (PT)* to ensure a therapeutic range of the *INR of 2–3.*
- Novel oral anticoagulants *do not require routine monitoring and dose adjustment*.

CASE 5: DEEP VEIN THROMBOSIS IN PREGNANCY

A 29-year-old female TN, with 7 months pregnancy presents with left leg swelling. Doppler USG shows femoral vein distended with fresh thrombus. She denies symptoms of cough, dyspnea and chest pain.

Qa. What is the most appropriate treatment for a pregnant woman who requires an anticoagulant therapy for deep vein thrombosis (DVT) for the rest of her pregnancy?

Low molecular weight heparin (LMWH) is the drug of choice for the management of DVT during pregnancy. Both LMWH and UFH are large molecular weight molecules that do not cross the placenta. Switching from LMWH to UFH may be considered during the last month of pregnancy as UFH has a shorter half-life and easy reversibility and so unwanted anticoagulant effect can be avoided.

Qb. Heparin-associated osteopenia and osteoporosis are rare but potentially serious complications of long-term heparin and LMWH therapy and often occurs during pregnancy and the postpartum period when it can result in spontaneous fractures. What is the underlying pathophysiological mechanism for osteoporosis? What precautions can be taken to prevent heparin-induced fractures?

Factors that contribute to heparin associated osteoporosis are overactivation of osteoclasts by parathormone, decreased activity of osteoblasts, increased bone resorption as a result of abnormal collagen activation and disturbances in vitamin D metabolism. Additionally, limited sun exposure during pregnancy and increased calcium demand during lactation can cause an osteoporotic state.

Adequate calcium and vitamin D supplementation is a prophylactic measure. It is also of note that LMWH presents less risk for osteoporosis than UFH and preferred for use.

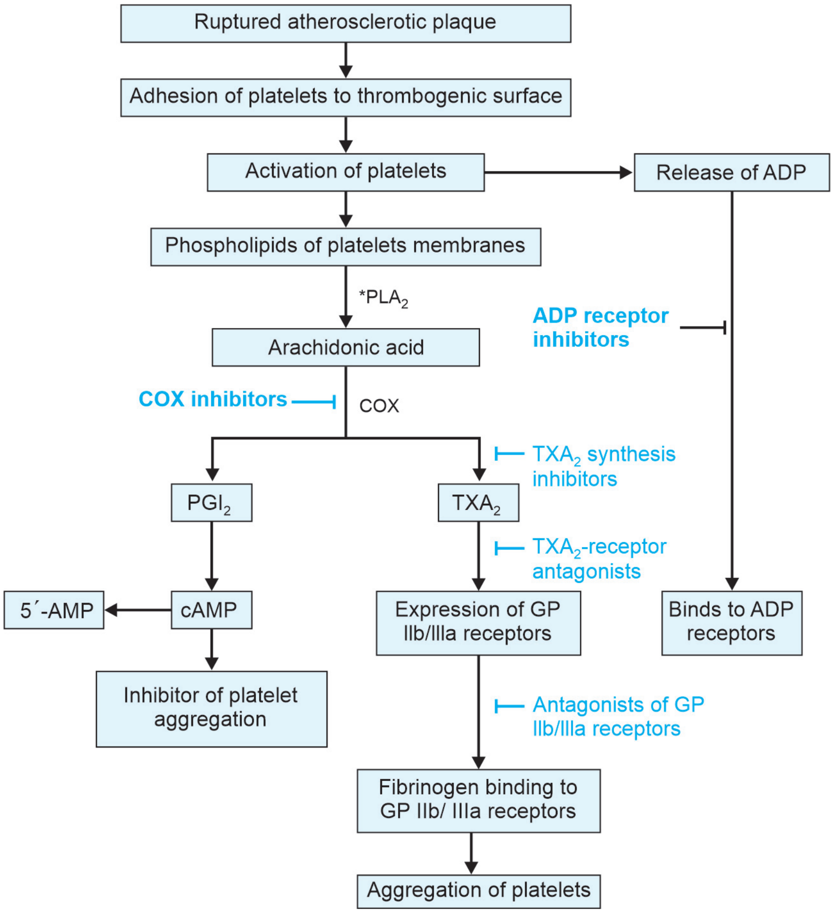
CASE 6: ACUTE CORONARY SYNDROME

Mr PQ, a 57-year-old male patient, suddenly awakened in the middle of the night with complaints of chest pain radiating to the left shoulder, shortness of breath and sweating. The patient was given 3 tablets of nitroglycerine at 5 min interval but there was no pain relief. Also he was given low dose aspirin 325 mg. Thereafter, he was transported to the nearby hospital.

Qa. How would you prescribe aspirin in case of heart attack as in PQ?

PQ experiences chest pain radiating to the left shoulder, shortness of breath and sweating. Patients with ongoing symptoms suggestive of myocardial infarction, should be encouraged to take low dose plain aspirin (non-enteric coated) 300–350 mg, orally. The tablet may be chewed to facilitate rapid buccal absorption or soluble aspirin tablets may be used.

Qb. Enlist the various antiplatelet drugs and mention how the drugs act to prevent and treat thromboembolic diseases.


Ruptured atherosclerotic plaque
Adhesion of platelets to thrombogenic surface
Activation of platelets
Release of ADP
Phospholipids of platelets membranes
*PLA2
ADP receptor inhibitors
Arachidonic acid
COX inhibitors
COX
TXA2 synthesis inhibitors
PGI2
TXA2
TXA2-receptor antagonists
5´-AMP
cAMP
Expression of GP IIb/IIIa receptors
Binds to ADP receptors
Inhibitor of platelet aggregation
Antagonists of GP IIb/IIIa receptors
Fibrinogen binding to GP IIb/ IIIa receptors
Aggregation of platelets

PLA_2: Phospholipase A_2, COX: Cyclo-oxygenase enzyme

Fig. 5.4: Atherosclerotic plaque rupture and thrombosis and actions of antiplatelet drugs

Antiplatelet drugs	*Mechanism of action*
I. Cyclo-oxygenase inhibitors Aspirin	Inhibition of COX enzyme prevents TXA_2 synthesis and inhibit platelet aggregation
II. Phosphodiesterase inhibitors Dipyridamole, cilostazole	Phosphodiesterase enzyme (PD) mediates conversion of cAMP to 5′-AMP. Inhibition of PD enzyme increases cAMP levels which is an inhibitor of platelet aggregation
III. $P2Y_{12}$ (ADP) receptor inhibitors clopidogrel, ticlopidine, prasugrel	Antagonize the action of ADP on ADP receptor, thereby inhibiting shape change and aggregation of platelets
IV. Antagonist of GPIIb/IIIa receptors (Abciximab, Tirofiban, Eptifibatide)	Prevents crosslinking of fibrinogen to GPIIb/IIIa receptors and inhibits platelet aggregation
V. Antagonist of TXA_2 receptors Terutroban	Blocks the binding of TXA_2 to the receptor and prevents TXA_2 action, that is, vasoconstriction and platelet aggregation

Qc. Explain the pharmacological basis of use of low dose aspirin in coronary artery disease.

The oral dose of plain aspirin (non-enteric coated formulation) should preferably be 75–300 mg once daily. TXA_2 initiates platelet aggregation and PGI_2 is an inhibitor of platelet aggregation. Low dose range of aspirin selectively inhibits thromboxane A_2-mediated platelet aggregation without affecting cyclo-oxygenase 2-dependent prostacyclin pathway. The resultant effect prevents blood clot formation in arteries and is useful in coronary artery disease.

Taken at high doses, aspirin acts as an anti-inflammatory agent by inhibiting COX-2 mediated endothelial production of prostacyclin PGI_2 which plays a key role in the inflammatory process.

Case Continued

He was rushed to primary health care centre where PCI facility was not available. Immediately ECG was performed and ECG of PQ showed ST-segment elevation myocardial infarction (STEMI).

The blood pressure reading was 150/100 mm of Hg. The time from the onset of symptoms was > 1 hr.

Qa. How would you differentiate ST elevation myocardial infarction from non-ST elevation myocardial infarction on the basis of ECG and cardiac biomarkers?

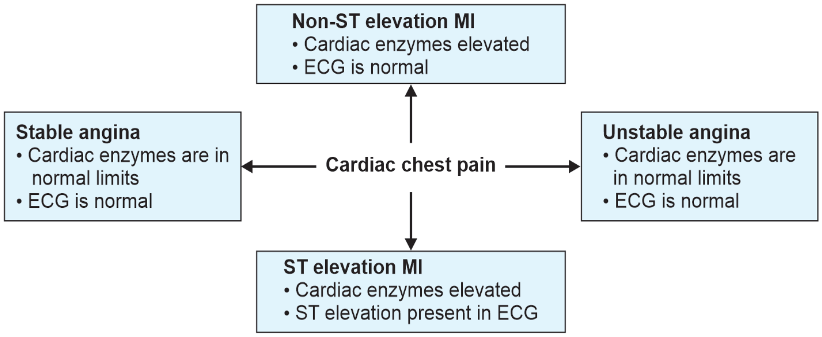

Non-ST elevation MI
• Cardiac enzymes elevated
• ECG is normal
Stable angina
• Cardiac enzymes are in normal limits
• ECG is normal
Cardiac chest pain
Unstable angina
• Cardiac enzymes are in normal limits
• ECG is normal
ST elevation MI
• Cardiac enzymes elevated
• ST elevation present in ECG

Fig. 5.5: Types of coronary artery disease: Effects on ECG and cardiac enzymes

In ST elevation myocardial infarction (STEMI), cardiac biomarkers troponin T and I are raised 20–50 times and ST segment is elevated on ECG.

In non-ST elevation myocardial infarction (NSTEMI) cardiac troponin T and I become detectable in blood and there is no ST-segment elevation on ECG.

Qb. What are the goals in the treatment of the patient PQ, a case of ST elevation myocardial infarction (STEMI)?

Goals of treatment:

1. To relieve symptoms
2. To limit the infarct size
3. Prompt reperfusion of the occluded artery

Case Continued

The treatment protocol for the patient PQ was as follows:

- **Intranasal oxygen was administered.**
- **IV nitroglycerine infusion 5 µg/min was started.**
- **10 U of reteplase (rPA) was administered as an intravenous bolus over 2 min, followed by a second bolus of 10U of rPA 30 min later**
- **Intravenous unfractionated heparin 4000 U IV bolus was injected**

- **Oral metoprolol tartrate 25 to 50 mg every 6 to 12 hours**
- **Clopidogrel (300 mg loading dose, followed by 75 mg daily) within 10 minutes of fibrinolytic administration**

Qa. What are thrombolytic drugs? How do they act?

Thrombolytic drugs dissolve blood clots by activating plasminogen to form plasmin, a proteolytic enzyme that is capable of breaking cross-links between fibrin molecules, which provide the structural integrity of blood clots. Because of these actions, thrombolytic drugs are also called 'plasminogen activators' and 'fibrinolytic drugs'.

Qb. What is tissue plasminogen activator (tPA)? Mention the commonly used 'plasminogen activators' or 'fibrinolytic drugs' used in the management of acute coronary syndrome.

Tissue plasminogen activator (tPA) is a naturally occurring fibrinolytic agent found in vascular endothelial cells and is involved in the balance between thrombogenesis and thrombolysis. It exhibits significant fibrin specificity and affinity. At the site of the thrombus, the tPA binds to the plasminogen attached to fibrin, activating plasminogen to plasmin which causes lysis of the clot.

The commonly used thrombolytics in acute coronary syndrome are streptokinase, reteplase and tenecteplase.

Qc. Compare the characteristic features of various drugs used for thrombolytic therapy in acute myocardial infarction.

Parameter	*Streptokinase (SK)*	*Reteplase (rPA)*	*Tenecteplase (TNK)*
Antigenic	Antigenic, elicits antibody formation	No	No
Allergic reactions (hypotension most common)	Allergic reactions occur (hypotension most common) Previous SK treatment or prior allergic reactions are contraindications	No	No
Fibrin specific	Non-fibrin specific, activates both fibrin bound and free plasminogen molecules	Yes	Yes
Systemic fibrinogen depletion	Marked	Moderate	Minimal
Systemic bleeding	Increased risk	Less risk	Less risk
Mode of administration	Short half life, given as infusion	Long half life, administered as bolus	Long half life, weight adjusted single bolus dose, less chance of medication error and ease of administration
90 min patency rates (%)	50 Approximately	75 Approximately	75 Approximately
Cost per dose (US dollars)	Cheap	Costly	Costly

Qd. Do you think it was appropriate to initiate fibrinolytic therapy in the patient PQ? If yes, give reasons.

Thrombolysis process works best on recently formed thrombi. Older thrombi have extensive fibrin polymerization. Hence, fibrinolysis is the most *effective and beneficial when given within first 2 hrs, in terms of reduction in death, stroke, serious bleed and infarct size.* Beyond this time, the efficacy diminishes and high doses are generally required to achieve desired lysis.

Qe. Why is reteplase (rtPA) preferred over streptokinase in the management of the patient PQ?

Reteplase (rtPA) is preferred over streptokinase in the management of the patient PQ due to the following reasons:

Streptokinase:

- Streptokinase is antigenic which leads to allergic reactions.
- It is non-fibrin specific and can catalyze systemic fibrinolysis forming fibrin degradation products and increased risk of bleeding.
- It has a short half-life and given as an infusion.

Reteplase:

- Reteplase is not antigenic and so there are no allergic manifestations.
- It is fibrin specific and is effective only on the surface of the fibrin clot with less systemic lysis state and is safer in preventing non-cerebral bleeds.
- It has a longer half-life which allows bolus administration and more convenient to be used in prehospital setting.
- It works faster compared to streptokinase or alteplase because reteplase does not bind fibrin as tightly as native tPA. It can diffuse more freely through the clot rather than bind only to the surface as tPA does. These characteristics help reteplase to resolve clots faster than streptokinase or alteplase.

Qf. What are the contraindications to be considered prior to initiating treatment with thrombolytics?

Absolute contraindications	*Relative contraindications*
• Previous ICH or stroke of unknown origin at any time	• Transient ischaemic attack in the preceding 6 months
• Ischaemic stroke in the preceding 6 months	• Oral anticoagulation therapy
• CNS damage or neoplasms or AV malformation	• Pregnancy or within 1 week postpartum
• Recent major trauma (surgery)/head injury (within the preceding 3 weeks)	• Refractory hypertension (systolic >180 mmHg and/or diastolic >100 mmHg)
• GI bleeding within the past month	• Advanced liver disease
• Known bleeding disorders (excluding menstruation)	• Infective endocarditis
• Aortic dissection	• Active peptic ulcer
• Non-compressible punctures in the past 24 h (e.g. liver biopsy, lumbar puncture)	• Prolonged or traumatic resuscitation

Qg. What are the benefits of administering antiplatelet drugs and anticoagulants alongside fibrinolytic drugs?

Administration of fibrinolytic drugs results in disintegration of clot and a paradoxical increase in local thrombin generation and enhanced ability of platelets to aggregate leading to rethrombosis and increased mortality from cardiovascular events.

Adjunctive antiplatelet (aspirin and clopidogrel) and anticoagulant therapy [unfractionated heparin, enoxaparin (LMWH) or fondaparinux)] with fibrinolysis reduces the risk of recurrent infarction and death in patients with ST-elevation myocardial infarction (STEMI).

Qh. Explain the rationale for prescribing beta blockers (metoprolol) in myocardial infarction as in PQ.

Beta-blockers confer the immediate benefit of reducing infarct size, increasing threshold for ventricular arrhythmias, and over the long term, preventing maladaptive ventricular remodelling and heart failure.

Qi. What caution needs to be considered prior to initiating treatment with beta blocker?

Patients with haemodynamic instability are at the greatest risk of developing cardiogenic shock associated with beta-blockers. Hence, oral β-blocker at low doses should be initiated, and an individualised approach should be followed.

Qj. Warfarin, an oral anticoagulant is not used in the management of acute coronary syndrome. Explain with reasons.

There is *delayed pharmacological action of warfarin.* Vitamin K-dependent carboxylation is essential for the synthesis of biologically active clotting factors (II, VII, IX and X) in the liver. *Warfarin blocks epoxide reductase resulting in depletion of reduced vitamin K and this interferes with the carboxylation and synthesis of clotting factors.* The pharmacological effect is not seen until all existing clotting factors are depleted from the circulation which relates to their half-life (3–4 half-lives are required for complete elimination from the body). This leads to delayed pharmacological effect of warfarin.

Warfarin has a *narrow therapeutic index* which requires monitoring plasma levels of the drug and exercising caution. Bleeding is the most serious and predictable toxicity of warfarin.

There is *risk of drug–drug interactions with warfarin* and hence caution is necessary.

Case Continued

Within 60 minutes, the symptoms had markedly decreased and there was ST-segment resolution by more than 50%. The haemodynamics was stable. The patient was then shifted to percutaneous intervention (PCI)-capable hospital and early PCI, that is, coronary angiography, with PCI of the infarct-related artery (IRA), 15 hours after fibrinolysis was performed.

Anticoagulant (unfractionated heparin) and antiplatelet (aspirin and P2Y$_{12}$ inhibitor) therapy was used during the procedure of PCI.

Qa. What are the benefits of unfractionated heparin therapy used during revascularisation procedure?

Unfractionated heparin (UFH) is routinely used for PCI. It is highly effective in reducing ischaemic events, death and recurrent myocardial infarction. The *short half-life, easy reversibility with protamine sulphate, non-renal clearance and the familiarity of clinicians with* *the drug* makes UFH the anticoagulant of choice in patients with renal failure, for patients with high risk of bleeding and those which require frequent intervention.

Qb. Enumerate the $P2Y_{12}$ inhibitors. How do they act as antiplatelet agents?

$P2Y_{12}$ inhibitors are categorized into thienopyridine (clopidogrel and prasugrel) and non-thienopyridine (ticagrelor) ADP $P2Y_{12}$ receptor inhibitors.

$P2Y_{12}$ inhibitors act by antagonizing the action of ADP on ADP receptor thereby inhibiting shape change and aggregation of platelets.

Qc. What is the role of $P2Y_{12}$ inhibitors in the management of coronary artery disease?

$P2Y_{12}$ inhibitors are administered as soon as possible in patients with STEMI, whereas prior to the procedure in patients with unstable angina or NSTEMI. They reduce infarct size, stent thrombosis and major adverse cardiac outcomes. However, they can increase the risk of bleeding.

Qd. How do you compare the effects of ticagrelor with clopidogrel in the management of ischemic heart disease?

i. Clopidogrel is an irreversible inhibitor of the $P2Y_{12}$ receptor while ticagrelor, a non-competitive direct-acting $P2Y_{12}$ receptor antagonist, binds reversibly to inhibit receptor signalling and subsequent platelet activation.

ii. Clopidogrel is a prodrug that is absorbed in the intestine and activated in the liver. The conversion of clopidogrel to its active metabolite requires two sequential oxidative steps. In contrast, ticagrelor is not a prodrug and does not require metabolism for activity.

iii. Ticagrelor has faster onset and causes more potent inhibition of platelet aggregation than clopidogrel. This results in reduced rates of thrombotic episodes compared to clopidogrel.

Qe. How are glycoprotein IIb/IIIa inhibitors useful in ischemic heart disease?

During an ischaemic event or during the procedure for PCI, there is activation of platelets leading to expression of glycoprotein receptors and fibrinogen crosslinking between the platelets resulting in their aggregation.

Glycoprotein receptor antagonists such as tirofiban, abciximab and eptifibatide inhibit fibrinogen binding and platelet aggregation. They have been used in the treatment of acute coronary syndromes as well as in the prevention of complications after percutaneous coronary interventions.

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Chapter

6

Drugs for Heart Failure

Qa. Define heart failure. Explain the various types of heart failure.

Heart failure develops when the heart, via an abnormality of cardiac function fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure.

Heart failure can be described as the following types:

- Low-output *vs* high-output heart failure
- Systolic dysfunction *vs* diastolic dysfunction
- Left-sided heart failure *vs* right-sided heart failure

Low Output *vs* High Output Heart Failure

Low-output-heart failure: It occurs when the heart is not able to pump adequate blood to meet the normal metabolic needs resulting in tissue hypoperfusion.

In ***high output heart failure***, the heart is healthy and pumps a normal or even higher than normal volume of blood. The metabolic demands of the body are high due to underlying medical disease such as hyperthyroidism, anaemia, pregnancy and there is inability of the heart to provide sufficient blood to keep up with the metabolic requirements of the tissues resulting in exhaustion of the heart.

Systolic Dysfunction *vs* Diastolic Dysfunction

In ***systolic dysfunction***, the heart fails to pump blood in the forward direction due to factors causing decreased myocardial contractility.

Systolic dysfunction is characterized by reduced stroke volume and cardiac output. The left ventricular ejection fraction (LVEF) is less than 40% and is termed as heart failure with reduced ejection fraction (HFrEF).

CO = SV × HR (normal cardiac output is 4–7 L/min, normal LVEF is 60–70%)

Left ventricular ejection fraction is defined as percentage of left ventricular end diastolic volume expelled during each systolic contraction.

In ***diastolic heart failure***, there are *abnormalities of left ventricle relaxation and/or filling*. Impaired relaxation causes elevation of left ventricular diastolic pressure at any given filling volume which leads to transmission of pressure to left atrium and pulmonary capillaries resulting in transudation of fluid into pulmonary interstitium.

Patients with diastolic heart failure commonly present with *normal or preserved ejection fraction (HFpEF) without any symptoms of heart failure.*

Possible causes of diastolic dysfunction include: Coronary ischaemia, chronic uncontrolled HTN, LV wall scarring after an MI, ventricular wall hypertrophy, hypertrophic cardiomyopathy, restrictive cardiomyopathy (amyloidosis and sarcoidosis), and valvular heart disease (aortic stenosis).

Left-sided Heart Failure *vs* Right-sided Heart Failure

In **left-sided heart failure,** the left ventricle of the heart no longer pumps enough blood into the body. As a result, blood builds up in the pulmonary veins. This causes shortness of breath, trouble-breathing or coughing, especially during physical activity.

In **right-sided heart failure,** the right ventricle of the heart is too weak to pump enough blood to the lungs. This causes blood to build-up in the veins of the periphery. The increased pressure inside the veins can push fluid out of the veins into surrounding tissue. This leads to build-up of fluid in the legs, or less commonly in the genital area, organs or the abdomen.

In **biventricular heart failure,** in biventricular heart failure, both sides of the heart are affected. This can cause the same symptoms as both left-sided and right-sided heart failure, such as shortness of breath and a build-up of fluid.

Qb. Enumerate the factors that determine heart failure.

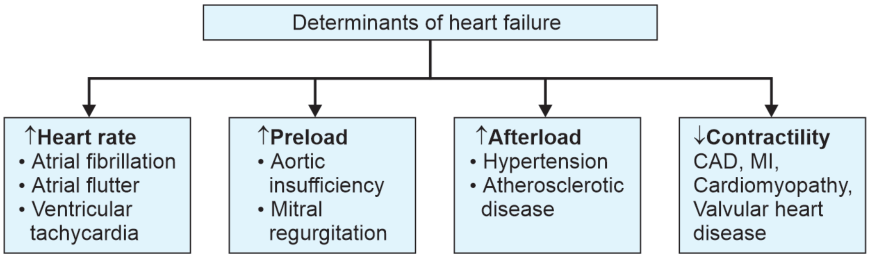
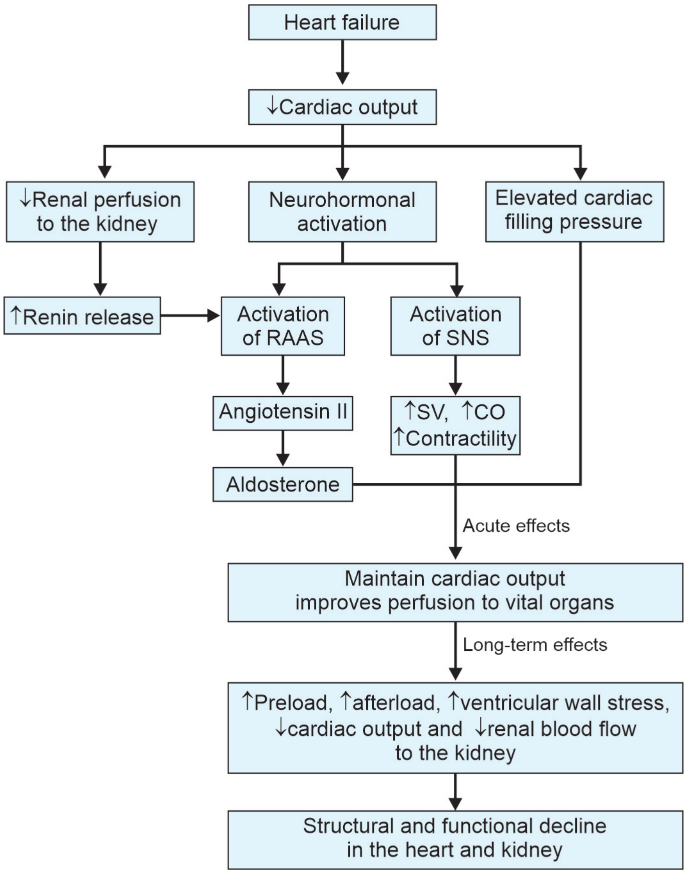


Fig. 6.1: Determinants of heart failure

1. *Increased heart rate:* Tachyarrhythmias including atrial fibrillation, atrial flutter, incessant supra-ventricular tachycardia and ventricular tachycardia are associated with cardiomyopathy that aggravates impaired systolic function and leads to progression of heart failure.
2. *Preload:* Also known as left ventricular end-diastolic pressure (LVEDPr), is the amount of ventricular stretch at the end of diastole. Conditions such as aortic insufficiency, mitral regurgitation, increase left ventricular filling during diastole leading to myocyte stretch causing a more forceful systolic contraction and increase in stroke volume. The Frank-Starling law relates to myocyte stretch and contractility. Thus, the forward stroke volume ejected by left ventricle depends on the degree of left ventricle filling during diastole.
3. *Afterload:* Also known as systemic vascular resistance (SVR), is the amount of resistance the heart must overcome to open the aortic valve and push the blood volume out into the systemic circulation.

4. *Decreased contractility:* Cardiac causes such as cardiomyopathy, valvular heart disease, scarring from ischaemia, can cause cardiac dysfunction and progression to heart failure.

Qc. Explain the compensatory mechanisms in heart failure with systolic dysfunction characterised by reduced cardiac output.


Heart failure
↓Cardiac output
↓Renal perfusion to the kidney
Neurohormonal activation
Elevated cardiac filling pressure
↑Renin release
Activation of RAAS
Activation of SNS
Angiotensin II
↑SV, ↑CO ↑Contractility
Aldosterone
Acute effects
Maintain cardiac output improves perfusion to vital organs
Long-term effects
↑Preload, ↑afterload, ↑ventricular wall stress, ↓cardiac output and ↓renal blood flow to the kidney
Structural and functional decline in the heart and kidney

SNS: Sympathetic nervous system; RAAS: Renin–angiotensin–aldosterone system; SV: Stroke volume; CO: Cardiac output

Fig. 6.2: Compensatory mechanisms and progression of heart failure

Congestive heart failure due to systolic dysfunction results in reduction in cardiac output and left ventricular ejection fraction. The fall in cardiac output leads to neurohormonal activation which includes stimulation of RAAS and sympathetic nervous system. Actually, these compensatory mechanisms maintain cardiac output and improve perfusion to vital organs by increasing cardiac contractility, arterial tone and LV preload.

However, over time increased preload, afterload and direct effects of angiotensin II and norepinephrine on the ventricular myocardium cause pathologic remodelling characterised by progressive chamber dilation and loss of contractile function. Decreased blood flow to the kidney leads to structural and functional changes in the kidney. These maladaptive effects on the cardiovascular and renal system, cause their functional decline or impairment in the long run.

Qd. What are the treatment strategies for the management of heart failure? Enumerate the drugs acting through these treatment principles.

Principle I: Neurohumoral Modulation

Drugs which modulate the neurohumoral system include:

a. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs)
b. Beta-blockers
c. Mineralocorticoid receptor antagonists
d. Angiotensin receptor neprilysin inhibitors (ARNI)

Principle II: Preload Reduction

Drugs:

e. Diuretics
f. Mineralocorticoid receptor antagonists

Principle III: Afterload Reduction

Drugs:

g. ACE inhibitors and ARBs
h. Nitrates: Nitroglycerine (predominantly venodilator), sodium nitroprusside
i. Hydralazine

Principle IV: Increasing Cardiac Contractility

Drugs:

j. Catecholamines: Epinephrine, norepinephrine, dopamine, dobutamine
k. Phosphodiesterase inhibitors: Amrinone, milrinone
l. Cardiac glycoside: Digoxin

Principle V: Reducing Heart Rate

Drugs:

m. Beta-blockers: Metoprolol, atenolol
n. Ivabradine

CASE 1: CASE OF ISOLATED DIASTOLIC HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION WITH ASSOCIATED RISK FACTORS FOR HEART FAILURE

RJ, 56-year-old male, presented with shortness of breath, unexplained sweating and chest pain on climbing stairs. There is history of persistent headache, difficulty in falling asleep for last few months.

Medical history: **Known case of 10-year history of diabetes mellitus and was on glimepiride and metformin. There is no history of MI, stroke, or peripheral artery disease in the past.**

Blood pressure (BP)—160/100 mmHg, glycosylated haemoglobin (HbA1c) level—7.4%, ECHO—shows features of left ventricular hypertrophy, diastolic dysfunction, LV ejection fraction 60%, NT-pro BNP—220 pg/ml, which is slightly elevated (upper limit of normal BNP is 100 pg/ml), eGFR—50 ml/min/1.73 m^2. Other lab investigations and haemodynamic data are normal.

Diagnosis/provisional diagnosis: **The patient RJ is diagnosed as a case of diastolic heart failure (grade II diastolic dysfunction) with uncontrolled hypertension, type 2 diabetes mellitus.**

Qa. Describe ACC/AHA staging scheme and the NYHA functional classification of heart failure. What stage of HF does RJ exhibit according to the American College of Cardiology/American Heart Association (ACC/AHA) criteria?

The ACC/AHA staging scheme and the NYHA functional classification of heart failure is shown below:

The ACC/AHA stages of heart failure	
A	At high risk for heart failure but without structural heart disease or symptoms of heart failure
B	Structural heart disease but without signs or symptoms of heart failure
C	Structural heart disease with prior or current symptoms of heart failure
D	Refractory end-stage heart failure requiring specialized intervention

New York Heart Association (NYHA) functional classification of heart failure	
I.	No limitation of physical activity
II.	Slight limitation of physical activity, in which ordinary physical activity leads to fatigue, palpitation or dyspnea; the person is comfortable at rest
III.	Marked limitation of physical activity, in which less than ordinary activity results in fatigue, palpitation, or dyspnea; the person is comfortable at rest
IV.	Inability to carry on any physical activity without discomfort but also symptoms of heart failure at rest, with increased discomfort if any physical activity is undertaken

According to *American College of Cardiology/American Heart Association (ACC/AHA)* criteria, RJ's case is classified as *Stage C* of heart failure, due to the presence of structural heart disease with signs and symptoms of heart failure. Haemodynamic data reveals there is no pulmonary congestion. Elevated serum BNP levels differentiate heart failure from non-cardiac conditions.

Qb. How severe is RJ's disability according to the New York Heart Association (NYHA) functional classification of HF?

RJ experiences shortness of breath, unexplained sweating and chest pain on climbing stairs. He is comfortable at rest. Mild symptoms and slight limitation during ordinary activity categorizes the functional disability of the patient as class II according to the New York Heart Association (NYHA) classification.

Qc. What are the other risk factors which predispose to heart failure?

Age, hypertension (HTN), myocardial infarction (MI), diabetes, tachycardia-induced cardiomyopathy, valvular heart disease, and obesity are well-established major risk factors associated with the development of HF. Other risk factors associated with HF are genetics, smoking, excessive intake of alcohol, dyslipidemia, anemia, and chronic kidney disease.

Qd. How does hypertension contribute to the structural changes in the heart and development of heart failure?

In hypertension, pressure overload leads to left ventricular hypertrophy (LVH), myocardial fibrosis, and impaired diastolic filling without systolic dysfunction.

In diastolic heart failure, there are *abnormalities of left ventricle (LV) relaxation and/or filling*. Impaired relaxation causes elevation of left ventricular diastolic pressure at any given filling volume which leads to transmission of pressure to left atrium and pulmonary capillaries resulting in transudation of fluid into pulmonary interstitium.

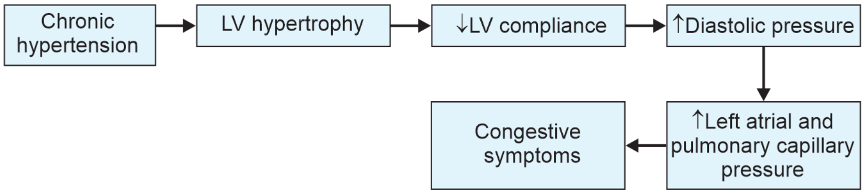


Fig. 6.3: Hypertension-induced structural changes in the heart and development of heart failure

Therefore, the therapeutic goal in diastolic heart failure is to improve left ventricular function and optimize haemodynamics, if symptoms of congestion are present.

Qe. What is the therapeutic goal and management of diastolic dysfunction in heart failure?

Therapeutic Goals

- Treat comorbidities
- Prevent heart failure symptoms
- Prevent further cardiac remodelling

Management

- Lifestyle modification such as weight loss, smoking cessation, dietary changes, limiting alcohol intake and exercise.
- Aggressive control of hypertension and diabetes
- Drugs for improving left ventricular function are beta-blockers, ACE inhibitors and angiotensin receptor blockers (ARBs), aldosterone receptor antagonists, angiotensin receptor and neprilysin inhibitors (ARNIs).
- Drugs for improving haemodynamics if the patient has congestive symptoms are diuretics and vasodilators.

CASE 2: HEART FAILURE WITH LEFT VENTRICULAR DYSFUNCTION AND REDUCED EJECTION FRACTION DUE TO UNDERLYING MITRAL REGURGITATION, AND RENAL INSUFFICIENCY

A 59-year-old male SK, with non-ischaemic dilated cardiomyopathy presents with shortness of breath and fatigue on exertion. No history of hypertension or diabetes mellitus, past cardiac illness. SK is a non-smoker.

Examination and investigations reveal: **HR—86/min, BP—98/70 mmHg, ECHO–ejection fraction = 30%, left ventricular filling pressure was elevated, his intraventricular cavity was dilated, CVP, pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) are moderately elevated, creatinine has risen from 1.2 to 3.3 and blood urea nitrogen from 20 to 52, coronary angiography—normal epicardial coronary blood vessels.**

Diagnosis: **This is a case of heart failure with reduced ejection fraction due to non-ischaemic dilated cardiomyopathy and impaired renal function.**

Treatment was initiated with 80 mg IV bolus of furosemide followed by a continuous IV infusion at a rate of 20 to 40 mg/hour.

Qa. Explain why treatment is initiated with furosemide diuretics.

Diuretics are an integral part of combination therapy of symptomatic heart failure. Diuretics such as furosemide act as venodilator. By increasing the venous capacitance, the venous return to the heart, end-diastolic volume and left ventricular filling pressure decrease. This causes shifting of fluid from pulmonary to systemic circulation and relieves symptoms of dyspnea. Also these agents inhibit Na^+-K^+-Cl^- symporter at the thick ascending limb of the loop of Henle resulting in brisk natriuresis and excretion of potassium and water. Through these mechanisms furosemide diuretics improve symptoms of congestive heart failure by moving patients to lower cardiac filling pressure along with the same ventricular function.

Qb. What are the common causes of diuretic resistance? Why treatment was initiated with high dose of intravenous furosemide in case of SK?

Congestive heart failure is usually associated with bowel wall edema and poor renal perfusion. Intestinal edema decreases the gastrointestinal absorption of drug and decreased perfusion results in insufficient delivery of drug concentration to the site of action of diuretics. These are common causes of diuretic resistance in heart failure and the response to diuretics in patients is less.

Therefore, to overcome diuretic resistance in congestive heart failure, intravenous loop diuretic at a higher dose or oral loop diuretic with greater oral bioavailability than furosemide may be used. Bumetanide and torsemide are more potent, have greater bioavailabilty and more predictable pharmacokinetics compared to furosemide. These drugs may be used as alternatives to furosemide.

Qc. The serum biochemistry values of SK show elevated levels of creatinine and BUN indicative of decline in renal function. Explain why loop diuretics are preferred over thiazide diuretics in heart failure associated with renal insufficiency.

Tubuloglomerular feedback (TGF) is a mechanism through which macula densa senses sodium chloride leaving the loop of Henle. If the concentration of sodium chloride is too high, the macula densa sends a signal to the afferent arteriole causing it to constrict, resulting in reduction in renal blood flow and glomerular filtration rate. This homeostatic mechanism serves to protect the organism from salt and volume wasting.

Furosemide increases intrarenal prostaglandin production, which plays a role in improving the renal parenchymal oxygen supply by decreasing the renal vascular resistance and increasing renal blood flow. Further, furosemide inhibits salt transport in the macula densa and macula densa can no longer detect or sense sodium chloride. This results in blockade of tubuloglomerular feedback mechanisms, which contributes in maintaining renal blood flow and GFR by blunting constriction of the afferent arteriole in heart failure associated with renal insufficiency.

Also at GFR <30–45 ml/min, there is less sodium reabsorption in the PCT compared to the normal condition, resulting in greater delivery of Na^+ to the nephrons distal to proximal tubule which facilitates more pronounced natriuretic effect of loop diuretics at the ascending limb of loop of Henle.

By producing brisk natriuresis, loop diuretics such as furosemide, improve congestive symptoms of heart failure, while maintaining the renal perfusion to the kidney. In contrast, thiazide diuretics act on the distal convoluted tubule (DCT), at a point past the macula densa, have little or no influence on tubuloglomerular feedback loop (TGF) and does not have much influence on renal blood flow.

Qd. If SK does not respond to furosemide diuretics, which are the other vasodilators that can produce haemodynamic improvement in heart failure? How do they work?

If the patient is refractory to diuretic therapy, the following drugs can be used to improve haemodynamics in heart failure and provide symptomatic improvement.

1. **Intravenous nitroglycerine:** Nitrates are often coadministered with diuretics in patients with congestive symptoms who fail to respond adequately to IV diuresis.

   Nitroglycerine predominantly dilates the veins, increasing venous capacitance, decreasing venous return to the heart, LV diastolic pressure and end-diastolic fibre length. Muscle shortening decreases myocardial oxygen consumption and work load on the heart (Frank-Starling law). Therefore, this is *specially beneficial in patients with heart failure resulting from acute myocardial ischaemia* in which case LV relaxation is impaired, LV compliance is decreased and LV diastolic pressure is elevated. However, long term use of intravenous nitroglycerine is avoided because of the potential for rapid development of tolerance.
2. **Sodium nitroprusside** administered parenterally acts on both the arterial and venous vessels reducing afterload, and preload, respectively. Nitroprusside is valuable in *severely congested patients with hypertension or severe mitral valve regurgitation* complicating LV dysfunction.
3. **Nesiritide** is recombinantly produced brain natriuretic peptide (BNP). Nesiritide increases the cGMP formation in the vascular smooth muscle with dilatation of arterial and venous blood vessels reducing afterload and preload, respectively.

Qe. Why should an individual on loop diuretic therapy be put on salt restricted diet?

Loop diuretics such as furosemide have short elimination t½ of 2 to 3 hrs. Furosemide produces significant natriuresis during the 6-hour period following drug administration. However, sodium excretion falls to very low levels during the remaining 18 hours of the day. As the concentration of loop diuretic in the tubular lumen declines, nephrons begin to avidly reabsorb sodium, increasing the concentration of sodium in the body and this effect often nullifies the overall effect of the loop diuretic on total body sodium. This is known as ***post-diuretic effect*** and can be overcome by restricting sodium intake or by more frequent administration of the loop diuretic or increasing the dose of diuretic.

Case Continued

In addition to furosemide, SK was started on treatment with an ACE inhibitor (ACEI), lisinopril, 10 mg per day.

Qa. How do ACE inhibitors act and what are the beneficial effects of ACE inhibitors in heart failure?

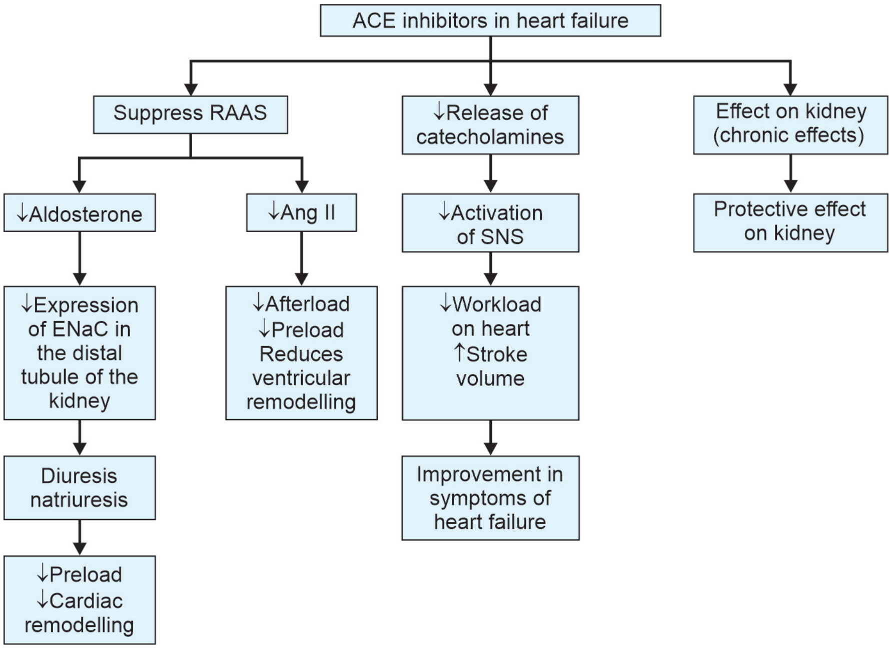
Angiotensin converting enzyme inhibitors (ACE inhibitors) modulate renin angiotensin aldosterone system by inhibiting angiotensin converting enzyme (ACE), preventing the conversion of angiotensin I to angiotensin II thereby reducing the circulating levels of angiotensin II.

Angiotensin II interacts with AT1 receptor to produce four major cardiovascular actions:

i. Vasoconstriction
ii. Stimulation of aldosterone release from adrenal gland
iii. Direct hypertrophic and proliferative effects on cardiomyocytes and fibroblasts, respectively
iv. Stimulation of norepinephrine release from sympathetic nerve endings and adrenal medulla

ACE inhibitors have the following beneficial actions:

1. **Reduction in afterload:** Decreased angiotensin II levels reverse the vasoconstriction, decreasing the impedence to LV ejection and thereby improves LV stroke volume.
2. **Reduction in preload:** Reduced aldosterone levels decrease the intravascular volume overload and improve hemodynamics in heart failure.
3. **Positive impact on ventricular remodelling** by lowering maladaptive effects on the cardiovascular system causing their functional decline or impairment in the long run due to reduced action of angiotensin II and aldosterone.
4. **Improve survival** in patients with heart failure due to systolic dysfunction.
5. **Reduced activation of sympathetic nervous system (SNS)** moderating the reflex tachycardia that accompanies vasodilation and lowering of blood pressure. This decreases myocardial oxygen demand and workload on failing heart producing beneficial action.
6. **Prevent structural and functional changes in the kidney** and provide protective action in long term.


ACE inhibitors in heart failure
Suppress RAAS
↓Release of catecholamines
Effect on kidney (chronic effects)
↓Aldosterone
↓Ang II
↓Activation of SNS
Protective effect on kidney
↓Expression of ENaC in the distal tubule of the kidney
↓Afterload ↓Preload Reduces ventricular remodelling
↓Workload on heart ↑Stroke volume
Diuresis natriuresis
Improvement in symptoms of heart failure
↓Preload ↓Cardiac remodelling

RAAS: Renin–angiotensin–aldosterone system; Ang: Angiotensin; SNS: Sympathetic nervous system; ENaC: Epithelial sodium channels

Fig. 6.4: Effects of ACE inhibitors in heart failure

Qb. Does combination of ACE inhibitors and ARBs have any beneficial effect on heart failure?

ACE inhibitors and ARBs administered concurrently do not have any additional benefits in heart failure but may increase the risk of hypotension, hyperkalemia and renal dysfunction, so there are no benefits of combination therapy in heart failure.

Qc. Explain why ACE inhibitors cannot fully suppress aldosterone levels though they act as an indirect aldosterone antagonist.

Plasma levels of aldosterone decrease under therapy with ACEIs or ARBs but quickly increase again. This phenomenon is called aldosterone escape.

Aldosterone escape occurs due to incomplete blockade of renin–angiotensin–aldosterone system (RAAS). Conversion of angiotensin I to angiotensin II and subsequent *aldosterone synthesis can also occur by action of chymase enzyme* which is an alternative pathway and is not inhibited by ACE inhibitors.

Aldosterone synthesis and secretion from the adrenal cortex is regulated not only by angiotensin II but also by plasma Na^+ and K^+. Therefore, *ACE inhibitors do not completely block the synthesis of aldosterone*.

Case Continued

If a patient who is under lisinopril treatment complains that he is bothered by dry and non-productive cough. He describes it as 'tickle at the back of the throat'. He noted that cough started 2 weeks after initiating lisinopril treatment. On chest examination, there is absence of wheezing and no evidence of pulmonary congestion. There is no past history of obstructive airway disease.

Qa. What is the likely cause of cough in the patient?

Cough presented by the patient can be a sign of heart failure with pulmonary congestion or due to bronchial asthma or as a side effect of ACE inhibitor. There is no prior history of bronchial asthma and chest examination, reveals absence of wheezing, so the cough is unlikely due to bronchial asthma. Continuation of lisinopril for a few more weeks will abate symptoms of heart failure leading to resolution of cough. If cough persists, it is possibly due to ACE inhibitor.

Qb. How do the ACE inhibitors induce cough? What should be the line of treatment for cough?

ACE inhibitors inhibit ACE enzyme which mediates degradation of bradykinin and substance P leading to accumulation of bradykinin and pro-inflammatory mediators such as substance P or prostaglandins in the upper airways causing cough.

Dose reduction or switch to another ACE inhibitor is not effective. ACE inhibitor should be discontinued and drug therapy should be switched to angiotensin receptor blocker (ARB). ARBs have the same physiological profile as ACE inhibitors except they do not induce cough or angioedema.

Qc. What is the underlying reason for angioedema with ACE inhibitors? What should be the line of action?

Angioedema can occur from use of ACE inhibitor in some patients. It is also due to accumulation of kinin resulting from ACE inhibition.

Angioedema can be treated by stopping the drug immediately and treating with H1 antagonist and corticosteroids.

Case Continued

Qa. You recommend that SK should be started on a β-blocker, metoprolol succinate (12.5 mg) before discharge. What is your rationale?

Beta-blockers antagonize excessive adrenergic stimulation on heart and provide the following benefits in heart failure:

- Beta-blockers have negative inotropic and chronotropic effect on the heart. This helps to control heart rate and prevent tachycardia thereby maximize the diastolic filling period and aid ventricular filling. Myocardial oxygen demand is reduced which is beneficial in myocardial ischaemia.

- These agents through inhibition of sustained sympathetic nervous activation promote regression of left ventricular hypertrophy, reduce catecholamine induced cardiomyocyte toxicity and apoptosis and decrease oxidative stress in the myocardium and thereby reduce left ventricular remodelling. This contributes in reducing morbidity and mortality in patients.
- They reduce automaticity thereby *decreasing the frequency of unstable tachyarrythmias* to which CHF patients are particularly prone and increase refractoriness at the AV node and helps to control the ventricular rate in atrial fibrillation associated with heart failure.
- Beta-blockers prevent inappropriate activation of renin–angiotensin–aldosterone system and its detrimental effects on heart because of reduced renin secretion resulting from sympathetic inactivation.

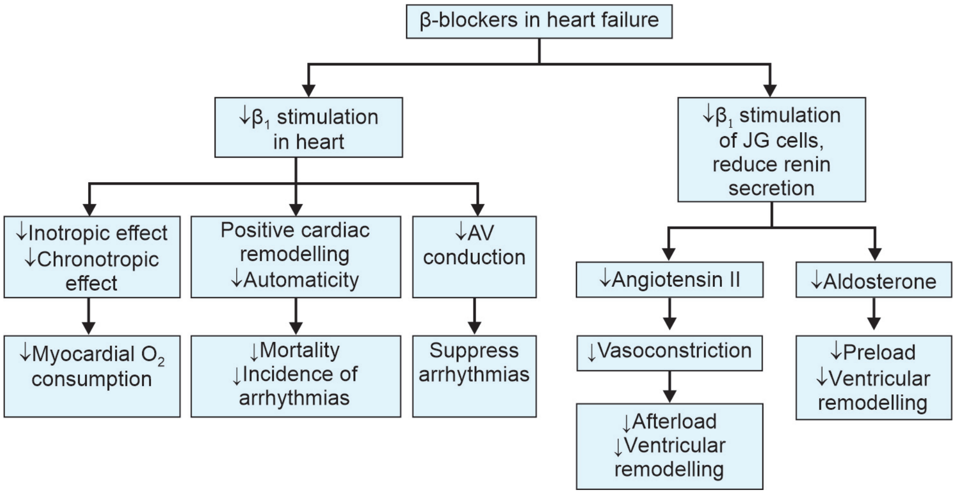

β-blockers in heart failure
↓β1 stimulation in heart
↓β1 stimulation of JG cells, reduce renin secretion
↓Inotropic effect ↓Chronotropic effect
Positive cardiac remodelling ↓Automaticity
↓AV conduction
↓Angiotensin II
↓Aldosterone
↓Myocardial O2 consumption
↓Mortality ↓Incidence of arrhythmias
Suppress arrhythmias
↓Vasoconstriction
↓Preload ↓Ventricular remodelling
↓Afterload ↓Ventricular remodelling

Fig. 6.5: Effects of beta-blockers in heart failure

Qb. What are the recommendations for the use of beta-blockers in heart failure as per ACC/AHA guidelines?

ACC/AHA guidelines recommend metoprolol succinate, bisoprolol or carvedilol to reduce morbidity and mortality in patients with current or prior symptoms of heart failure with reduced ejection fraction (HFrEF) in conjunction with an ACE inhibitor or AT_1 receptor antagonist, and diuretics as required to palliate symptoms.

Qc. Why β1-selective agents and carvedilol are preferred agents in heart failure with reduced ejection fraction?

Metoprolol and bisoprolol are β1-selective agents, and carvedilol is a non-selective β-blocker with additional α1-blockade and antioxidant property. Beta-1 selective blockers have less or no action on β2-receptors and hence have limited bronchoconstrictive or vasoconstrictive properties.

Carvedilol has beneficial antioxidant property but has been reported to cause hypotension and dizziness because of its additional α1-blockade action. Hence, metoprolol and bisoprolol are preferred β-blocker agents in heart failure patients with hypotension.

Qd. What are the principles of initiating treatment with β-blockers in heart failure?

Principles of initiating treatment with beta-blockers are the following:

1. Therapy to be initiated in a clinically stable condition and at very low doses (1/8th of target)
2. Dose escalation with time, doubling at 4 week in ambulatory settings. Thus, *start low and go slow* in the treatment of heart failure with beta-blockers.

Under these conditions, the heart has time to adapt and function at lower adrenergic drive under the influence of adrenergic blockade. Importantly, beta-blockers do not fully block the receptors rather they are competitive antagonists that shift the concentration response curve of catecholamines to the right which means that the beta-blocker can be displaced from its receptor by increasing catecholamine concentrations.

Qe. Explain why β-blockers should not be administered in new onset or acutely decompensated heart failure.

Beta-blockers are usually not administered in new onset heart failure because in the initial phase of heart failure there is activation of sympathetic nervous system as a compensatory mechanism which increases stroke volume, cardiac output and improves peripheral perfusion. This is beneficial in heart failure and hence blockade of sympathetic nervous system would have a negative outcome on heart failure. So, the use of β-blockers is not recommended in the early stage of heart failure.

In acute decompensated heart failure, positive inotropic support of catecholamines is essential to augment cardiac output and maintain circulatory support. Administration of β-blocker will further inhibit the failing heart worsening the clinical condition of heart failure.

Qf. What is the rationale behind combining diuretics with ACE inhibitors or beta-blockers in the management of patient with heart failure?

Diuretics promptly reduce left ventricular preload. This can lead to a reflex neurohormonal stimulation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone axis (RAAS). Activation of these pathways contribute to the pathophysiology of heart failure, thus potentially undermining the benefits of diuretic use. Also importantly, diuretics have failed to show mortality benefit in heart failure patients.

Concurrent treatment with ACE inhibitors and beta-blockers will produce *neurohormonal blockade and reduce mortality* which may improve outcome in patients with heart failure.

Case Continued

2 years later, the patient SK, presented to the outpatient department with complaints of fatigue on exertion despite maximal therapy with furosemide—40 mg daily, enalapril—5 mg BID, metoprolol succinate—12.5 mg daily.

On examination: **Blood pressure and pulse rate are normal, LVEF is 38%, haemodynamic data and laboratory investigations are normal.**

The physician decides to replace enalapril, an ACE inhibitor with ARNI (sacubitril/valsartan).

Qa. What is ARNI? What are the beneficial effects of ARNI?

ARNI is angiotensin receptor–neprilysin inhibitor. Neprilysin is a peptidase which causes degradation of protective peptides (BNP, ANP, CNP) and renin–angiotensin–aldosterone system (RAAS) is an important neurohormonal stressor system. A favourable approach is to inhibit neprilysin and RAAS axis (Ang II/ACE/AT1R) which increases protective BNP levels and also provides the advantages of RAAS blockade.

Initially, ACE inhibitor was combined with neprilysin inhibitor (ACEi/NEPi), e.g. omapatrilat and was found to be protective in heart failure and CKD but resulted in increased frequency of angioedema. Thus, the development of ARNI was undertaken which had the beneficial effects of Ang II receptor-blockers and neprilysin inhibitors (NEPi) with less risk of angioedema.

Thus ARNI promotes beneficial effects of natriuresis, diuresis, and vasodilatation of arterial and venous blood vessels. It inhibits thrombosis, fibrosis, cardiac myocyte hypertrophy and renin release.

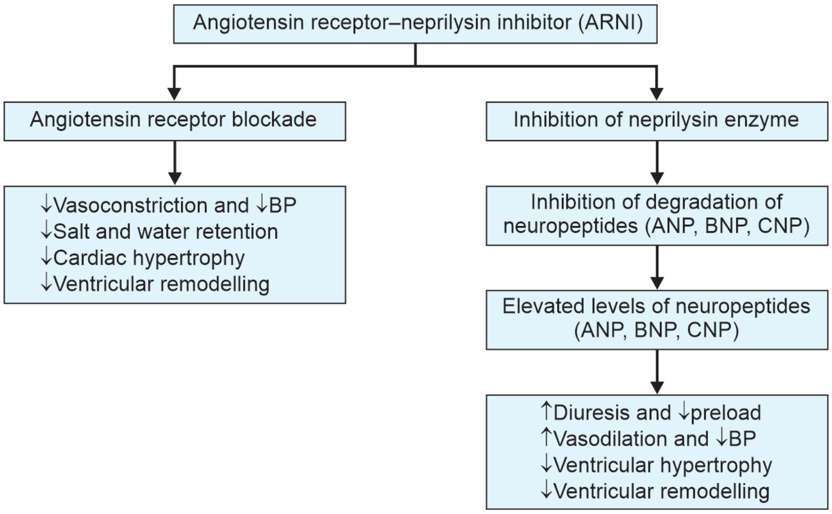

Angiotensin receptor–neprilysin inhibitor (ARNI)
Angiotensin receptor blockade
Inhibition of neprilysin enzyme
↓Vasoconstriction and ↓BP
↓Salt and water retention
↓Cardiac hypertrophy
↓Ventricular remodelling
Inhibition of degradation of neuropeptides (ANP, BNP, CNP)
Elevated levels of neuropeptides (ANP, BNP, CNP)
↑Diuresis and ↓preload
↑Vasodilation and ↓BP
↓Ventricular hypertrophy
↓Ventricular remodelling

Fig. 6.6: Effects of angiotensin receptor–neprilysin inhibitor (ARNI) in heart failure

Qb. Instead of ARNI, can spironolactone, an aldosterone receptor antagonist be added to the treatment regimen of the patient SK for better control of symptoms? If yes, explain how aldosterone antagonist is useful in the management of heart failure.

Aldosterone receptor antagonist acts as an antagonist at nuclear receptors of aldosterone. They are K^+ sparing diuretics but gained more importance in the treatment of heart failure for their additional efficacy in suppressing the consequences of neurohumoral activation. It has been documented to have a life-prolonging effect in patients with heart failure.

Qc. Is it safe to combine aldosterone antagonist with ACE inhibitor or ARB?

Aldosterone receptor antagonist is a potassium sparing diuretic and ACE inhibitors cause potassium retention. Combination of aldosterone antagonist with ACE inhibitor or ARB is expected to increase the risk of hyperkalemia but studies have revealed that the combination is safe. It should be given in low doses (25 mg) to all patients in stage C (NYHA II to IV) as it is known to decrease mortality in heart failure patients.

Qd. What precautions should be considered prior to initiating treatment with an aldosterone receptor antagonist?

The following precautions are taken during initiation of treatment with aldosterone receptor antagonist:

- Administer no more than 50 mg/day (maximum dose in heart failure)
- Do not use if GFR is <30 ml/min
- Be careful in elderly patients because in such cases prevention of side effects is more important than improvement of prognosis
- Be careful with diabetics who carry a higher risk of hyperkalemia
- Do not combine with NSAIDs which are contraindicated in heart failure
- Do not combine with other K^+ sparing diuretics

Qe. What are the hormonal adverse effects that would be anticipated in this patient if treated with spironolactone?

Spironolactone is a non-specific steroid hormone receptor antagonist with similar affinity for progesterone and estrogen receptor.

Gynaecomastia is reported in 10% of men treated with spironolactone and dysmenorrhea is common in women because of antagonistic actions of spironolactone on androgen, estrogen or progesterone receptors.

Qf. Which drug can be used as an alternative to spironolactone to avoid hormonal side effects?

Eplerenone, an aldosterone antagonist is approved for the treatment of heart failure. Eplerenone is selective for the aldosterone receptor with minimal action on estrogen and progesterone receptors, so related hormonal side effects such as gynaecomastia and sexual dysfunction may be less.

Qg. Mention the side effect which is common to both spironolactone and eplerenone.

Most important adverse effect which is common to both spironolactone and eplerenone is hyperkalemia.

CASE 3: DECOMPENSATED HEART FAILURE WITH RENAL INSUFFICIENCY

A 68-year-old man TN, with type II diabetes mellitus and ischaemic cardiomyopathy (left ventricular ejection fraction, 25%) presents with dyspnea despite compliance with optimal medical therapy (enalapril and metoprolol succinate).

CVP, pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) is significantly elevated. His creatinine is risen from 1.2 to 2.3 and his blood urea nitrogen from 20 to 52.

You decide to admit him to the hospital for further treatment, including intravenous loop diuretics. Dopamine infusion was initiated at a dose of 1 µg/kg/min.

Qa. Explain the rationale for the use of low dose of dopamine (0.5–2 µg/kg/min) in heart failure associated with renal insufficiency as in case of SK.

Low dose dopamine (0.5–2 µg/kg/min), dilates renal blood vessels increasing renal blood flow, improving renal perfusion and thereby maintain an adequate GFR, in the setting of heart failure with impaired renal function refractory to diuretics.

At intermediate infusion rates (2–3 µg/kg/min), dopamine directly stimulates cardiac β1-receptors and accelerates myocardial contractility leading to tachycardia.

At higher infusion rates (5–15 µg/kg/min), there is increased α-receptor-mediated peripheral arterial and venous constriction resulting in increased afterload.

Intermediate and high doses of dopamine increases cardiac workload on the failing ventricle which is undesirable and, therefore, low doses of dopamine is recommended to improve renal function in heart failure.

Qb. Explain the acute effects and chronic effects of ACE inhibitors or ARBs on kidney function.

GFR depends on the intraglomerular pressure which is maintained by balance between the afferent flow into the glomerulus and efferent flow exiting the glomerulus. When the renal perfusion to the kidney decreases due to hypovolemia or decrease in cardiac output, RAAS is activated increasing the angiotensin II action on the efferent arteriole. *Vasoconstriction mediated by angiotensin II plays a key role in preserving the glomerular pressure* and maintaining optimal GFR and has a beneficial action on the kidney.

Acute effects of ACE inhibitors: Administration of ACE inhibitors in low flow or low pressure states removes the protective action of angiotensin II on the kidney and leads to sudden lowering of GFR resulting in an increase in serum creatinine.

Chronic effects of ACE inhibitors: ACE inhibitors have afterload reducing properties which increases the stroke volume and cardiac output enhancing the renal blood flow improving the GFR and in long term results in a decline in structural and functional changes in the kidney exerting a protective action on the kidney.

Qc. Explain why caution is advised with use of ACE inhibitors or ARBs in heart failure associated with advanced renal insufficiency (GFR <30 ml/min).

Although ACE inhibitors or ARBs are renoprotective and are used in heart failure with reduced ejection fraction, they are used with careful monitoring of blood pressure, renal function and electrolyte levels.

ACE inhibitors have the potential to raise serum potassium levels through inhibition of aldosterone release and its action on the renal tubules. This effect is significant in renal insufficiency leading to dangerous hyperkalemia.

ACE inhibitors are associated with hypotension and worsening of renal function in situations where fall in blood pressure is not followed by increase in cardiac output or renal blood flow. They may decrease GFR and increase creatinine by 20 to 30%.

The guidelines recommend caution when prescribing ACEIs/ARBs in patients who have low systolic blood pressure (80 mm), increased serum creatinine (>3 mg/dl), bilateral renal artery stenosis or serum potassium > 5 mEq/L.

Qd. Comment on combination therapy with hydralazine and isosorbide dinitrate in heart failure patients with reduced ejection fraction and who cannot receive ACE inhibitors due to intolerance or contraindication.

The hydralazine–isosorbide dinitrate (ISDN) combination has arterial and venous vasodilating properties and thus reduces afterload and preload. Hydralazine is mainly an arterial dilator, and hence lowers the systemic vascular resistance causing an increase in stroke volume. This represents a reduction in afterload.

Isosorbide nitrate is predominantly a venodilator, and therefore reduces venous return, end-diastolic volume and pressure. This decreases the wall stress that occurs within the left ventricle during ventricular filling. This represents a reduction in preload. Reduction in both preload and afterload decreases the symptoms of heart failure that are due to either pulmonary vascular congestion or to inadequate forward cardiac output.

Furthermore, hydralazine and isosorbide dinitrate combination has antioxidant property. It has a beneficial effect on endothelial dysfunction and improves NO bioavailabilty. Hydralazine prevents nitrate tolerance by reducing reactive oxygen species (ROS)-mediated inactivation of nitric oxide.

Qe. What is the role of ivabradine in the treatment of heart failure with reduced ejection fraction (HF-rEF)?

Ivabradine is a heart rate (HR) reducing agent and can be used in the management of patients with heart failure and reduced ejection fraction (HF-rEF), with the objective to reduce heart failure hospitalizations.

It is recommended if the left ventricular ejection fraction is ≤35%, heart rate ≥70 bpm in sinus rhythm and there are persisting symptoms (NYHA class II-IV) despite treatment with an evidence-based dose of a β-blocker (or maximum tolerated dose), an angiotensin converting enzyme inhibitor (or angiotensin-receptor blocker) and a mineralocorticoid receptor antagonist.

Ivabradine exerts its heart rate (HR) reducing effect, through selective inhibition of the funny current (inward Na^+/K^+ current), mediated by the hyperpolarization-activated cyclic nucleotide-gated channels (HCN). This selective HR reduction decreases myocardial oxygen demand and increases diastolic duration, allowing increased coronary flow and thus improving oxygen supply without directly affecting inotropy.

CASE 4: HEART FAILURE WITH VERY LOW CARDIAC INDEX AND PULMONARY HYPERTENSION

A 52-year-old woman admitted to the hospital with ischaemic cardiomyopathy (left ventricular ejection fraction, 25%) complains of progressive fatigue and dyspnea. Heart rate is 95 bpm and blood pressure 95/60 mmHg. Creatinine is stable at 1.4. Haemodynamic data shows elevated pulmonary artery pressure (65/28 mmHg), pulmonary capillary wedge pressure (25 mmHg) and right atrial pressure of 14 mmHg. Cardiac index is low (1.4).

The patient's condition fails to improve despite receiving IV furosemide and nitroglycerine.

The physician decides to use an inotropic agent to improve the clinical condition of the patient.

Qa. How are the inotropic agents beneficial in acute decompensated heart failure?

Inotropic agents directly enhance myocardial contractility increasing the stroke volume improving organ perfusion and simultaneously reduce left and right heart filling pressure and pulmonary congestion. This provides short-term benefit on haemodynamics and symptomatic improvement.

Qb. What are the available inotropic agents in the management of acute heart failure? How do the inotropes act in heart failure patients?

The following inotropic agents are available for the management of ***acute heart failure:***

I. Cyclic AMP-dependent Inotropes

These include:

1. Catecholamines/sympathomimetics: Epinephrine, norepinephrine, dopamine and dobutamine

The catecholamines act via stimulation of cardiac β1-receptor-mediated stimulation of adenylyl cyclase–cyclic AMP-PKA pathway. Protein kinase A causes phosphorylation of a number of substrates which increases calcium entry and raises sarcoplasmic reticulum calcium, synchronizing the release of calcium that enhances Ca^{2+}-dependent myocardial contraction (positive inotropic effect) and relaxation (positive lusitropic effect) allowing sufficient perfusion of the ventricle in diastole.

2. Phosphodiesterase inhibitors/non-sympathomimetics: Amrinone, milrinone

The drugs inhibit the action of phosphodiesterase enzyme, thus reducing the breakdown of cyclic AMP in the cardiac and vascular tissues resulting in cyclic AMP-mediated stimulation of *increased contractility* (positive inotropic effect) and *dilation of arteriolar and venous blood vessels* with subsequent reduction in afterload and preload, therefore known as *inodilators.*

II. Myofilament Calcium Sensitizer: Levosimendan

These drugs increase the affinity of the myofilaments for calcium by inducing a conformational change in troponin C, resulting in increased contractility and positive inotropic action.

Qc. Digoxin is the only inotropic agent used in chronic stable heart failure. How is the mechanism of action of digoxin different from the inotropic agents used in acute heart failure?

Unlike the cyclic AMP-stimulating therapies, digoxin loads the sarcoplasmic reticulum with calcium by blocking sarcolemmal pump which regulates the extrusion of Na^+ outside the myocyte in exchange for K^+.

Inhibition of Na^+-K^+-ATPase enzyme leads to accumulation of Na^+ in the sarcoplasma, decreasing the Na^+ gradient across the myocyte membrane and thus reducing the driving force for Ca^{2+} extrusion by the sodium calcium exchanger.

This increases the intracellular concentration of calcium. Calcium is transported into the sarcoplasmic reticulum, where it is stored during diastole. When the next depolarising impulse reaches the myocyte, a greater quantity of calcium is released, resulting in enhanced contractility. This accounts for the positive inotropic action of digoxin.

Qd. What are the problems associated with use of catecholamines as inotropic agents in heart failure?

Problems associated with catecholamines include tachycardia, induction of dysrhythmias, and unsuitable vasoconstriction. Catecholamines also have a role in maladaptive remodelling.

Epinephrine in addition to positive inotropic action also exhibit positive chronotropic effect. Excessive increase in heart rate increases the cardiac workload and myocardial oxygen demand in the setting of a failing ventricle.

Norepinephrine is most likely associated with marked vasoconstriction resulting in increased preload and afterload with poor tissue perfusion.

Dopamine rather than selectively increasing renal perfusion and cardiac output may also cause tachycardia due to stimulation of cardiac β1-receptors.

Qe. Among the available catecholamines (epinephrine, norepinephrine, dopamine and dobutamine), explain why dobutamine is the best inotropic agent.

Dobutamine is the inotropic agent of choice in heart failure because of the following reasons:

- Dobutamine is a selective β1-agonist with negligible or no action on β2 or α-receptors. It increases cardiac contractility and output, improving blood flow to organs and reducing the congestive symptoms.
- It has little chronotropic action and so does not increase the workload of heart significantly which is beneficial to a failing heart.
- It has no action on α-receptors so there is no vasoconstriction or increase in peripheral vascular resistance. This allows sufficient perfusion to various organs.

Qf. How is milrinone superior to catecholamines in improving haemodynamics in heart failure patients?

Both milrinone and catecholamines act via stimulation of β-receptors and eventually through cyclic AMP-dependent phosphorylation of calcium handling proteins, increase calcium entry via L type voltage calcium channels. This raises calcium in the sarcoplasmic reticulum, causing synchronized release of calcium into the cytoplasm which accelerates myocardial contraction and thereby provide inotropy and short-term haemodynamic benefits in heart failure. But compared to catecholamines, milrinone has predominant vasodilatory action, causing dilatation of arterial and venous blood vessels, reducing the systemic vascular resistance, thus decreasing preload and afterload and improving tissue perfusion. Milrinone has a favourable effect on oxygen balance in the failing ventricle and is less likely to produce tachycardia or dysrhythmias.

Qg. Should milrinone be administered in heart failure patients with renal insufficiency?

Milrinone is primarily cleared by renal excretion and is avoided in patients with acute renal failure or end-stage renal disease. Thrombocytopenia may also be a problem with milrinone use.

Qh. What are the risks associated with cyclic AMP stimulating therapies such as catecholamines and phosphodiesterase inhibitors?

It is important to note that cyclic AMP-stimulating therapies, namely catecholamines and phosphodiesterase inhibitors are associated with more adverse events during hospitalization and an increased postdischarge mortality. Cyclic AMP stimulation has also been implicated in maladaptive remodelling. Therefore, they are used for short-term haemodynamic benefit in heart failure.

CASE 5: DIGOXIN THERAPY IN HEART FAILURE

A 62-year-old man with ischaemic cardiomyopathy and a left ventricular ejection fraction of 30% is seen in follow-up after his second hospitalization for heart failure this year. Despite adherence to maximal medications and strict sodium and fluid restrictions, he continues to complain of exertional fatigue.

The physician added 0.25 mg digoxin daily.

Qa. How is digoxin beneficial in heart failure?

The benefits provided by digoxin in heart failure are as follows:

- **Haemodynamic benefits:** Due to positive inotropic action which increases the force of systolic contraction of heart muscle and improves cardiac output and ejection fraction. *Duration of systole is reduced and time for ventricular filling and relaxation is increased.* Diastolic size of the heart is reduced and there is a decrease in cardiac workload and increase in exercise tolerance.
- **Neuromodulatory action:** Due to digoxin-induced inhibition of sympathetic nervous system activity and renin-angiotensin system because of baroreceptor sensitization. However, this action is less marked in digoxin than with ACEIs in heart failure patients.
- **Vagomimetic action:** Slows conduction of impulses at atrioventricular (AV) node and plays a role in controlling ventricular rate in atrial fibrillation that is why digoxin is preferred in heart failure associated with atrial fibrillation.
- Digoxin therapy has been shown to ***decrease heart failure hospitalizations.***

(Of note, *digoxin has not been shown to provide mortality benefit* when used in the setting of heart failure with reduced ejection fraction.)

Qb. What is the mechanism of action responsible for positive inotropic action of digoxin?

Digoxin binds to and blocks sarcolemmal Na^+-K^+-ATPase pump which regulates the extrusion of Na^+ outside the myocyte in exchange of K^+.

Inhibition of Na^+-K^+ ATPase enzyme leads to accumulation of Na^+ in the sarcoplasma, decreasing the Na^+ gradient across the myocyte membrane, reducing the driving force for Ca^{2+} extrusion by the sodium-calcium-exchanger (NCX).

This increases the intracellular concentration of Ca^{2+}. Calcium is transported into the sarcoplasmic reticulum where it is stored during diastole. When the next depolarising impulse reaches the myocyte, a greater quantity of Ca^{2+} is released, resulting in a more forceful contraction during excitation-contraction coupling accounting for the positive inotropic action of digoxin.

CASE 6: A CASE OF CHRONIC DIGOXIN TOXICITY

A 65-year-old woman PQ, presented to the clinic with a major depressive disorder and treatment initiated with paroxetine 20 mg/day.

Medication history: **She had an episode of atrial fibrillation 2 years ago and is on 0.25 mg digoxin daily and 1 mg warfarin daily for 2 years.**

2 days later, she presented with nausea, vomiting, dizziness and chest pain. Later, she developed delirium with visual hallucinations and disorientation.

Laboratory examination showed elevated creatinine indicating impaired renal function. There was no electrolyte derangement.

ECG showed many ventricular premature contractions and complete AV block.

Digitalis intoxication was suspected, serum digoxin concentration 5–2 ng/ml (normal range 0.5–2.0 ng/ml).

Qa. How is digoxin useful in the management of atrial fibrillation as in patient PQ?

Digoxin is indicated in patients with chronic atrial fibrillation for restoration of sinus rhythm, prevention of recurrence and slowing of the ventricular rate. It has a negative chronotropic action on the sinus node and vagomimetic effect on the atrioventricular node. This contributes to a decrease in heart rate and slows down atrioventricular conduction velocity and is useful in controlling the ventricular rate in atrial fibrillation.

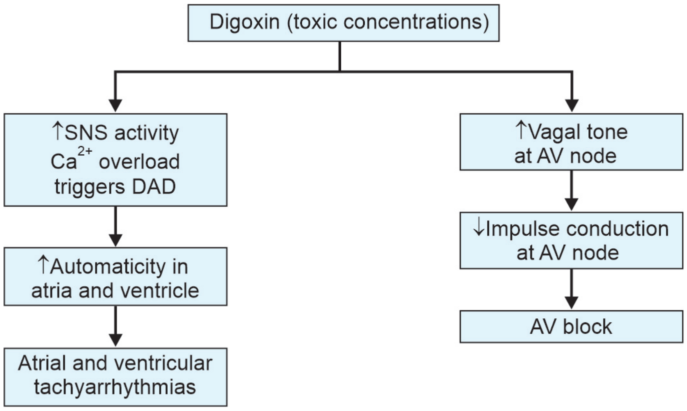
Qb. What are the extracardiac clinical manifestations observed in PQ that relate to digoxin toxicity?

The patient PQ presents with gastrointestinal side effects such as anorexia, nausea, vomiting and diarrhea and central nervous system side effects like headache, weakness, dizziness, apathy, confusion and mental disturbances (anxiety, depression, delirium and hallucination). These are the common extracardiac manifestations of digoxin toxicity.

Qc. How do you explain the ECG findings indicating ventricular premature contractions and complete AV block caused by digoxin overdose?

Digoxin has important parasympathetic effects particularly on the AV node. Increased vagal tone at the AV node increases the effective refractory period which in turn reduces the conduction velocity at the AV node. This can lead to AV block at high concentrations of digoxin.

With toxic concentrations of digitalis, there can be increased activation of sympathetic nervous system and Ca^{2+} overload in the sarcoplasmic reticulum with spontaneous release into the cytoplasm. This triggers delayed afterdepolarization (DAD) which leads to the generation of atrial and ventricular arrhythmias. Ventricular arrhythmias are among the most common rhythm disturbances caused by digoxin toxicity and include unifocal and multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation.


Digoxin (toxic concentrations)
↑SNS activity
Ca2+ overload
triggers DAD
↑Automaticity in atria and ventricle
Atrial and ventricular tachyarrhythmias
↑Vagal tone at AV node
↓Impulse conduction at AV node
AV block

SNS: Sympathetic nervous system; DAD: Delayed afterdepolarization

Fig. 6.7: Effects of high concentration of digoxin

Qd. How do renal function and electrolyte disorders influence digoxin toxicity?

Digoxin is primarily excreted by the kidneys, therefore dose adjustment is required in renal failure. Elderly patients should be given smaller loading and maintenance doses because of smaller body size and decreased renal function.

Digoxin toxicity may occur in patients with hypokalemia or hypomagnesemia because potassium or magnesium depletion sensitizes the myocardium to digoxin. Hypercalcemia also predisposes the patient to digitalis toxicity.

Qe. How is digoxin toxicity treated?

Supportive care for digoxin toxicity includes hydration with IV fluids, oxygenation and support of ventilatory function, discontinuation of the drug and sometimes correction of electrolyte imbalances.

Gastrointestinal Decontamination and Enhanced Elimination

The first-line treatment for acute ingestion is repeated dosing of activated charcoal to reduce absorption and interrupt enterohepatic circulation. Binding resins such as colestyramine or colestipol may be used to break enterohepatic circulation.

Treatment of Electrolyte Imbalances

Correct hypokalaemia, hyperkalaemia and hypomagnesemia. Correction of electrolyte imbalances may reverse dysrhythmia.

Digoxin Immune Therapy

Digoxin immune Fab is an immunoglobulin fragment that binds with digoxin. It is currently considered first-line treatment for significant dysrhythmias from digitalis toxicity.

Management of Dysrhythmias

In hemodynamically stable patients, bradyarrhythmias and supraventricular arrhythmias may be treated with observation and supportive care. In hemodynamic instability, digoxin Fab fragments are the treatment of choice, short-acting beta-blockers (e.g. esmolol) may be helpful for supraventricular tachyarrhythmias with rapid ventricular rates. Calcium channel blockers are contraindicated because they increase digoxin levels.

Premature ventricular contractions (PVCs), bigeminy and trigeminy may require only observation unless the patient is haemodynamically unstable, in which case lidocaine may be effective. Ventricular tachycardia response is best to digoxin immunotherapy but lidocaine and phenytoin are useful if immune therapy is ineffective or unavailable.

Atropine may be useful in digoxin-induced effects of enhanced vagal tone on the SA node and AV node. It has proved helpful in reversing severe sinus bradycardia.

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Chapter 7

Antiarrhythmic Drugs

CASE 1: CASE OF ATRIAL FIBRILLATION WITH ASSOCIATED HEART FAILURE

A 55-year-old male patient TD with BMI 33 kg/m^2 presents to the emergency department with complaints of uncomfortable racing heart beats, dizziness and shortness of breath. His LVEF is 35%. On examination, pulse rate is 155 beats/min and is irregularly irregular, blood pressure 110/60 mm, and respiratory rate 25/min. Chest examination suggests bilateral rales. There is mild edema in both legs. Neck veins are distended. ECG shows absence of P wave and irregular QRS.

Past medical history suggests he has undergone cardiac bypass surgery following an ischaemic attack 2 years back. The patient is a known case of diabetes and hypertension and is on medications.

Your diagnosis: **Atrial fibrillation with associated heart failure.**

Q1a. What is cardiac 'arrhythmia'? How do you classify various types of arrhythmias based on the 'origin of impulse generation'?

Cardiac arrhythmia is defined as disturbance of initiation or conduction of cardiac impulse. Arrhythmias can be classified based on origin of impulse generation:

1. Supraventricular arrhythmias are arrhythmias originating above the bundle of His, i.e. from atria, SA node or AV node. These may include sinus bradycardia, sinus tachycardia, paroxysmal supraventricular tachycardia, atrial flutter, atrial fibrillation (AF), Wolff-Parkinson-White (WPW) syndrome, and premature atrial contractions (PACs).
2. Ventricular arrhythmias are arrhythmias originating below the bundle of His, i.e. from the ventricles. These include premature ventricular contractions (PVCs), VT, and ventricular fibrillation (VF).

Qb. Considering the clinical data available for TD, do you think TD is experiencing arrhythmia? If yes, classify the type of arrhythmia based on the origin of impulse generation.

The patient TD has a pulse rate of 155 beats/min and the pulse is irregularly irregular with symptoms of uncomfortable racing heart beats, dizziness and shortness of breath. ECG shows absence of P wave and irregular QRS. Thus, the clinical findings suggest that the patient TD is a case of '*atrial fibrillation*' which is classified as '*supraventricular arrhythmia*' since the impulse originates above the bundle of His.

Qc. What is the pathway of propagation of electrical impulse in a normal heart?

In a normal cardiac cycle, an electrical impulse initiates at the SA node, propagates through the atria to enter the AV node, where conduction is slowed. This allows the ventricle to fill up with blood before ventricular contraction. Subsequently, the impulse enters the His–Purkinje system, which quickly activates the ventricular myocardium and triggers contraction of the heart. A variation in the sequence of cardiac impulse propagation gives rise to arrhythmias.

Qd. What are the signs and symptoms observed in TD, that are consistent with atrial fibrillation?

Atrial fibrillation is characterised by an irregular and often rapid heart rate that occurs when many unstable electrical impulses misfire and may result in the atria quivering out of control. There is lack of synchronization between the heart cells. This results in fast and irregular heart rhythm. The heart rate in atrial fibrillation may range from 100 to 175 beats per minute. Abnormal movement of the electrical signals result in improper filling-up of different chambers of heart with blood to be pumped out to the body. As a result, cardiac output is low. This leads to poor perfusion and symptoms which include heart palpitations, shortness of breath and weakness as seen in the patient TD.

Q2a. What is meant by 'transmembrane potential'?

Transmembane potential is maintained with the interior of the cell negative with respect to outside the cell. This is caused by unequal distribution of ions between the inside and outside the cell. Na^+ and Ca^{2+} ions are higher outside and K^+ ions are higher inside the cell. Potentials are maintained by ion selective channels, active pumps and exchangers. The action potential generation occurs by movement of ions across the membrane.

Qb. Explain the underlying ion currents responsible for different phases of the action potential in a normal cardiac tissue in response to a stimulus.

i. Non-pacemaker cells example ventricular myocyte
ii. Pacemaker cells example sinus node

Various phases and underlying ion currents in different phases of the action potential in normal ventricular myocyte (non-pacemaker cell) in response to stimulation:

Phase	*Underlying ion currents*
Phase 4 (resting membrane state)	• Electrochemical gradient caused by the unequal distribution of ions on the either side of the membrane maintains the resting membrane potential at 90 mV negative to the exterior which is close to the equilibrium potential of K^+
Phase 0 (rapid depolarization/ fast upstroke)	• Fast inward Na^+ current (approximately 10^7 Na^+ ions enter and the surge of Na^+ ions lasts for approximately 1 millisecond) • Phase 0 ends with the inactivation of Na^+ channels
Phase 1 (rapid short repolarisation)	• Characterised by a little 'notch', that corresponds to transient outward K^+ current
Phase 2 (plateau phase)	• Inward Ca^{2+} current balanced by the outward K^+ current (the rise in intracellular Ca^{2+} concentration mediates contraction of heart muscles)
Phase 3 (phase of repolarization)	• Large outward K^+ current through delayed rectifier K^+ channel causes repolarization of the membrane to its resting level

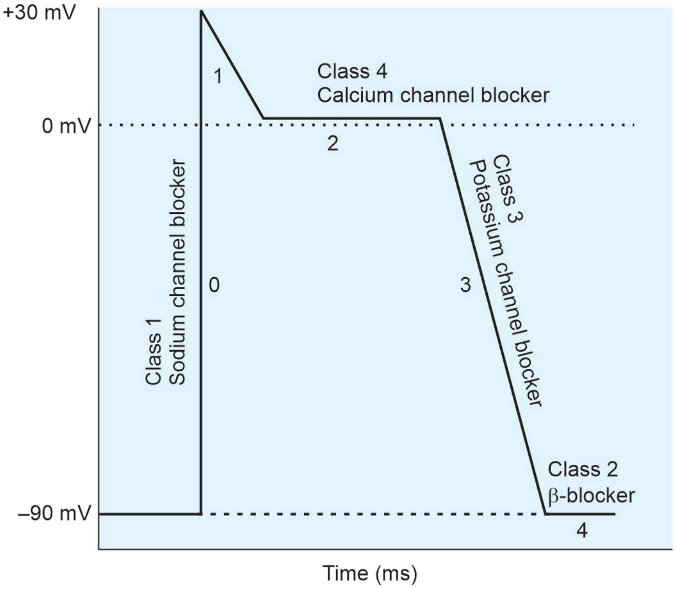


Fig. 7.1: Action potential of normal ventricular myocyte

Various phases and underlying ion currents in different phases of the action potential in normal SA node (pacemaker cell) action potential:

Phase	*Underlying ion currents*
Phase 4 (slow depolarisation)	• Leakage of Na^+ ions into the cell through the funny channels which gradually depolarize the membrane potential to the threshold (Phase 4 is the primary determinant of automaticity and heart rate and depends mainly on funny current)
Phase 0 (action potential upstroke)	• Action potential upstroke caused by inward Ca^{2+} current through voltage sensitive L-type Ca^{2+} channels
Phase 3 (phase of repolarisation)	• Repolarization of the membrane mediated by delayed rectifier outward K^+ current

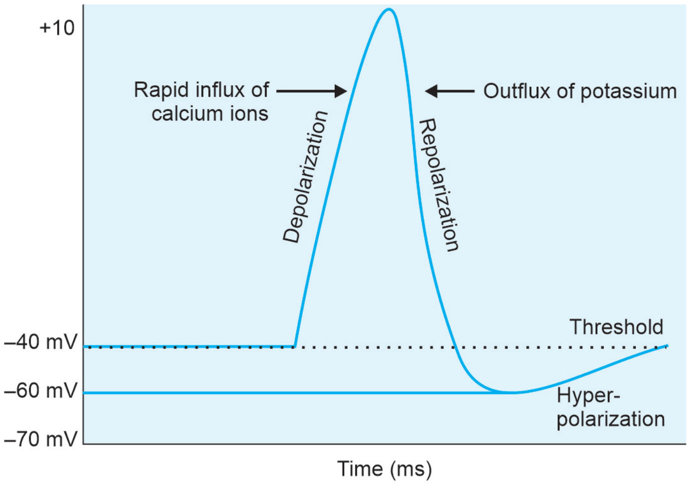


Fig. 7.2: Action potential of normal SA node

Qc. Give the Vaughan-William classification scheme of antiarrhythmic agents. Mention the basis of such classification.

The antiarrhythmic medications have been categorized according to the Vaughan-William classification system. The system classifies the medications according to the main mechanism of action (although several of the agents retain properties from multiple classes).

Class of drug	*Drugs*	*Mechanism of action*
Class I (sodium channel blockers)		
• **Class Ia** (medium affinity block)	Quinidine, procainamide, disopyramide	• Cause moderate phase 0 depression and moderately suppress conduction • Prolong repolarization
• **Class Ib** (low affinity block)	Lidocaine, phenytoin, mexiletine, tocainide	• Cause weak phase 0 depression and have little influence on conduction velocity • Slightly shorten repolarization
• **Class Ic** (high affinity block)	Flecainide, propafenone, encainide, morcizine	• Cause marked phase 0 depression and markedly slow conduction • Have little effect on repolarization
Class II (beta-blockers)	Propranolol, metoprolol, esmolol	• Suppress automatic discharge (phase 4 depolarisation) • Decrease SA nodal and AV nodal conduction velocity • Increase effective refractory (ERP) period at the AV node
Class III (prolongation of repolarisation)	Amiodarone, dronedarone, bretylium, sotalol, dofetilide, ibutilide	• Prolong repolarization (phase 3) • Prolong action potential duration (APD) and effective refractory period (ERP) in all cardiac tissues • No effect on conduction velocity of the impulse
Class IV (calcium channel blockers)	Verapamil, diltiazem	Predominant action in the SA node and AV node: • Suppress automaticity in pacemaker cells • Increase effective refractory period (ERP) and slow conduction velocity

Miscellaneous antiarrhythmic drugs outside the Vaughan-William classification scheme: Adenosine, digitalis, potassium, magnesium.

Q3a. The heart rate of the patient TD diagnosed with atrial fibrillation is 155 beats/min and the pulse is irregularly irregular. How does defect in impulse formation alter automaticity, contributing to arrhythmia?

Defective impulse formation can lead to altered automaticity which includes enhanced normal automaticity or disturbance in overdrive suppression.

Enhanced Normal Automaticity

The SA node is called the heart's 'natural pacemaker'. The electrical impulse begins in the SA node and the electrical activity spreads throughout the atrium causing it to contract. Enhanced automaticity of pacemaker cells can increase the rate of action potential discharge. The rate of abnormal automaticity is substantially higher than that of normal automaticity and is a sensitive function of resting membrane potential (that is, the more depolarized is the resting potential, the faster the rate of discharge).

Overdrive Suppression of Automaticity

The SA node continuously generates electrical impulses, thereby setting the normal rhythm and rate in a healthy heart. Pacemaker cells are also located in the AV node, bundle of His and Purkinje fibres. Under normal conditions, all subsidiary pacemakers are overdrive suppressed by SA nodal activity. In abnormal conditions, automaticity can be altered, when latent pacemaker cells takeover the SA node's role as the pacemaker of the heart and the rate of firing of latent pacemaker cells is faster than the SA nodal rate.

Qb. Mention the electrophysiological changes in the cardiac tissue that determine increased firing rate associated with arrhythmias.

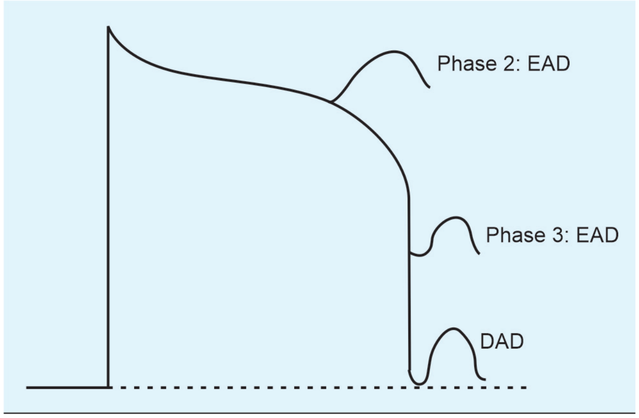
The following electrophysiological changes in the cardiac tissue determine increased rate of firing associated with certain arrhythmias:

- *Faster phase 4 depolarization* due to opening of greater number of pacemaker channels that mediate funny sodium current, so that the threshold potential is quickly reached at the end of phase 4.
- A *negative shift in the threshold potential*, so that threshold potential is quickly achieved and this increases the excitability of the membrane.
- A *positive shift in the maximum diastolic potential (resting potential)* which increases the rate of firing because less time is needed to repolarise the membrane fully at the end of phase 3.

Qc. How does 'triggered activity' or 'afterdepolarizations' play a role in the genesis of cardiac arrhythmia?

Afterdepolarizations occur when a normal action potential triggers extra-abnormal depolarizations. That is, the first normal action potential triggers additional oscillations of membrane potential which may lead to arrhythmia. There are two types of afterdepolarizations:

1. Early afterdepolarization (EAD)
2. Delayed afterdepolarization (DAD)



EAD: Early afterdepolarisation, DAD: Delayed afterdepolarisation

Fig. 7.3: Triggered activity or afterdepolarizations

1. Early Afterdepolarization (EAD)

- Phase 2 (plateau phase) or phase 3 (rapid repolarization phase) of normal action potential is interrupted by abnormal depolarization. If the depolarisation reaches the threshold potential, an abnormal impulse generates which triggers the development of arrhythmia.
- Results from inhibition of delayed rectifier K^+ current leading to marked prolongation of action potential (AP) and development of a type of arrhythmia termed 'torsades de pointes'.
- This is common at slower heart rates and low extracellular potassium.
- Treatment goal is to shorten the action potential duration (APD) by increasing the heart rate by pacing or isoproterenol infusion because increase in heart rate causes shortening of action potential duration (APD).
- Magnesium is the drug of choice for suppressing early afterdepolarizations (EADs) and terminating the arrhythmia.

2. Delayed Afterdepolarization (DAD)

- Afterdepolarizations occur after full repolarization of the normal action potential. This depolarization if exceeds threshold potential becomes an action potential.
- The abnormal depolarization is due to Na^+ entry in exchange of Ca^{2+} through sodium calcium exchanger (Na-Ca-X).
- DAD is caused by calcium overload states such as digitalis toxicity, myocardial infarction and heart failure.
- The risk is more at higher heart rates.

Qd. Given that the patient TD is in heart failure with symptoms of low cardiac output and LVEF of 35%, do you think heart failure could have contributed to the development of atrial fibrillation? If yes, explain which type of triggered activity may be responsible for arrhythmia in TD.

Heart failure may lead to delayed afterdepolarizations (DAD) which could have triggered the development of arrhythmia in the following ways:

1. Upregulation of Na^+–Ca^{2+} exchanger (NCX) which causes Na^+ entry in exchange of Ca^{2+} resulting in depolarization and generation of abnormal impulse.
2. Altered intracellular calcium regulation due to downregulation of key regulators of intracellular Ca^{2+} including the ryanodine receptor and the sarcoplasmic reticulum Ca^{2+}-ATPase in heart failure. These effects may create a state of atrial intracellular diastolic Ca^{2+} overload which contributes to the generation and maintenance of atrial fibrillation.

Q 4. Outline the management strategy of atrial fibrillation.

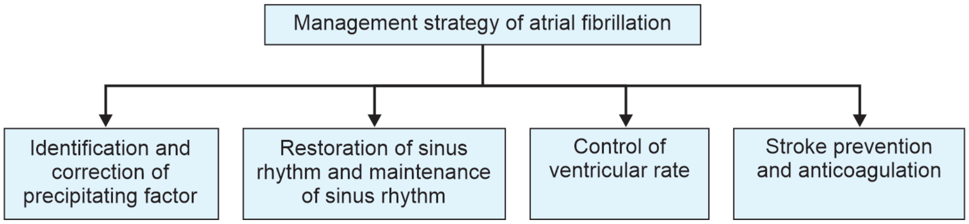

Management strategy of atrial fibrillation
Identification and correction of precipitating factor
Restoration of sinus rhythm and maintenance of sinus rhythm
Control of ventricular rate
Stroke prevention and anticoagulation

Fig. 7.4: Management strategy of atrial fibrillation

i. Identification and correction of precipitating factor

Therapy should be directed towards the primary abnormality such as fever, pneumonia, alcoholic intoxication, thyrotoxicosis, electrolyte disturbances, hypotension, pulmonary emboli, congestive heart failure or pericarditis.

ii. Restoration of sinus rhythm and maintenance of sinus rhythm

The most effective method of cardioversion is by direct current (DC) cardioversion. In situations where electrical cardioversion is undesirable or the patient is not willing, pharmacologic cardioversion may be attempted.

In patients with no coronary artery disease (CAD) or structural heart disease, class Ic antiarrhythmic medications such as oral flecainide and oral propafenone are the mainstay for rhythm control.

In patients with structural heart disease such as CAD, heart failure or hypertrophy of heart, amiodarone, a class III agent can be used to restore and maintain sinus rhythm.

iii. Control of ventricular rate

When clinical condition is unstable or patient is hemodynamically compromised, immediate electrical cardioversion is the treatment of choice. In the absence of cardiovascular compromise, slowing of ventricular rate with drugs becomes the therapeutic goal.

Digoxin, beta-adrenergic blockers (propranolol, metoprolol and sotalol), non-dihydropyridine calcium channel blockers (verapamil and diltiazem) and adenosine are AV nodal blockers and are effective in controlling the ventricular rate in atrial fibrillation or flutter. Amiodarone also decreases SA and AV nodal conduction which may improve atrial fibrillation with rapid ventricular rate.

iv. Stroke prevention and anticoagulation

Atrial fibrillation, especially when long lasting, increases the risk of atrial clot formation and systemic thromboembolism. The patients should receive an anticoagulant (unfractionated heparin, low-molecular-weight heparin, factor Xa, or direct thrombin inhibitor) as soon as possible surrounding the cardioversion, followed by long-term anticoagulation.

Q 5a. How are the sodium channel blockers useful in the treatment of atrial fibrillation as in case of TD?

The sodium channel blockers act in the following ways to suppress arrhythmia.

1. Effect on slope of phase 4 of action potential in nodal tissues and amplitude of phase 0 of action potential in non-nodal tissues

Slow Na^+, 'funny' pacemaker current in cardiac nodal tissue determines the rate of depolarisation (phase 4, pacemaker potential) and in non-nodal tissues fast inward Na^+ current determines the speed of propagating action potentials (amplitude of phase 0 and V_{max}).

Hence, Na channel blockers decrease the slope of phase 4 of pacemaker currents, delay spontaneous diastolic depolarisation and suppress enhanced normal automaticity-induced arrhythmias. They also decrease the conduction velocity in non-nodal tissues (atrial and ventricular muscle, Purkinje-conducting systems) which is an important mechanism for suppressing tachycardias.

2. Effect on threshold potential

Excitability and automaticity in cardiomyocytes depends on threshold potential. Threshold potential is the intracellular negativity at which abrupt and complete depolarisation occurs and is –70 mV in normal cardiac tissue. Quinidine like drugs raise the threshold potential, that is, the threshold potential becomes less negative, and thereby suppress automaticity and excitability of cardiac tissue.

Qb. How would you manage sodium-channel blocker poisoning?

Sodium channel blockers act by slowing sodium influx into myocytes through voltage gated channels. Sodium channel blocker poisoning is associated with high death rates. Sodium bicarbonate or lactate, increasing serum pH and extracellular concentration of the ion, displaces the drug from its receptor sites and can be used for the treatment of cardiac toxicity in the setting of sodium channel blocker poisoning.

At faster heart rates, the sodium channel block increases which enhances the effect of Na^+ channel blockers. Hence, beta-blockers by reducing the heart rate can decrease steady state sodium channel block and its associated toxicity.

Q6a. Although quinidine is useful in restoring sinus rhythm in atrial fibrillation, it can predispose the patient to 'torsades de pointes' a polymorphic type of ventricular tachycardia. Explain how.

Quinidine due to its sodium channel blocking action has the following beneficial effects in the management of atrial fibrillation:

- Inhibition of funny sodium current of phase 4 in the nodal tissues (pacemaker potential) helps to restore and maintain the sinus rhythm in atrial fibrillation.
- Inhibition of fast inward sodium current of phase 0 of the action potential in non-nodal tissues slows down the conduction velocity of electrical impulses and controls tachycardia.

However, quinidine also blocks delayed rectifier K^+ channel responsible for K^+ efflux and repolarisation. This results in prolongation of action potential duration and increase in QT interval and may precipitate the onset of torsades de pointes, a type of ventricular tachycardia caused by early afterdepolarizations.

In addition, the refractory period at SA node and AV node is modified by the anticholinergic property of quinidine which is most prominent at SA node and AV node because of extensive innervation by vagal efferent nerves. The vagal inhibitory action of quinidine results in both an increase in sinoatrial rate and an increase in atrioventricular conduction contributing to its proarrhythmogenic effect.

Thus, quinidine (class Ia drug) can induce secondary arrhythmias and this is often precipitated by hypokalemia or hypomagnesaemia, increasing the mortality rate when used in atrial fibrillation for rhythm maintenance.

Qb. Can procainamide belonging to class Ia also induce torsades de pointes similar to quinidine?

Procainamide is less likely to induce torsades de pointes (TdP) due to its predominant sodium channel blocking effect with minimal K^+ channel blocking property. However, it can induce TdP in patients with renal dysfunction or in rapid acetylators because its active metabolite, N-acetyl procainamide (NAPA) has a potential K^+ channel blocking effect.

Qc. Quinidine administration in atrial flutter may be associated with disastrous consequences. Explain with reasons.

In the absence of quinidine treatment, atrial flutter rate of 300 b/min with AV node transmission in the ratio 2:1 or 4:1 decreases the heart rate to 150 b/min or 75 b/min. Quinidine has vagal inhibitory activity that enhances AV conduction with AV nodal transmission rate of 1:1. Therefore, an atrial flutter rate of 220 b/min causes a heart rate of 220 b/min due to the transmission of all the impulses to the ventricle, resulting in an increase in ventricular rate and ventricular tachycardia with disastrous consequences.

Qd. Why is digoxin administered before quinidine use in the management of atrial fibrillation?

Digoxin has vagomimetic action and increases the refractory period at the AV node reducing the conduction of impulses at the AV node. This counterbalances the effect of quinidine which enhances AV conduction due to its vagolytic action. Therefore, digoxin is administered before quinidine to prevent the conversion of atrial fibrillation or flutter into paradoxical ventricular tachycardia.

Qe. What are the non-cardiac side effects of quinidine? What is the effect of quinidine on digoxin concentration when co-administered?

The non-cardiac side effects of quinidine include allergic reactions, diarrhoea, thrombocytopenia and cinchonism at high doses. Cinchonism is characterised by signs and symptoms of blurred vision, tinnitus, headache, psychosis, and gastrointestinal upset.

Quinidine increases the digoxin concentration by displacing digoxin from tissue binding sites and decreasing renal clearance of digoxin due to the inhibitory action of quinidine on P-glycoprotein, an energy-dependent efflux transporter which pumps drug molecules out of the cells. The reduced clearance of digoxin increases the half-life of the drug and increases the risk of toxicity.

Qf. What is pseudobulbar affect? What is the therapeutic basis for the use of quinidine in the management of pseudobulbar affect?

Pseudobulbar affect is a disorder of emotional regulation characterized by uncontrollable outbursts of laughing and/or crying that are disproportionate to the emotions being experienced. The emotional outbursts are being generated autonomously in the brainstem due to loss of regulatory control by the frontal lobe.

Combination of dextromethorphan and quinidine sulphate can be used in the treatment of pseudobulbar affect. Quinidine is a potent inhibitor of CYP2D6 hepatic enzymes which plays a role in the metabolism of dextromethorphan. This slows down the metabolism of dextromethorphan and increases dextromethorphan bioavailability and efficacy in the treatment of pseudobulbar affect.

Qg. What are the side effects expected with disopyramide use? What are the limitations for the use of disopyramide in heart failure?

Disopyramide has significant anticholinergic property which is more than quinidine and results in many of its adverse effects. These include dry mouth, urinary retention, constipation and precipitation of glaucoma.

The negative inotropic action of disopyramide may reduce contractile force up to 42% at low doses and up to 100% in higher doses leading to heart failure or exacerbation of heart failure.

Qh. Why is procainamide administered as slow IV for restoring sinus rhythm in atrial fibrillation? Why long-term therapy with oral procainamide is poorly tolerated?

Procainamide is administered as slow IV to avoid hypotension due to ganglionic blockade which can occur at higher doses and with rapid infusion rates.

Procainamide is metabolized into N-acetyl procainamide (NAPA) in the liver by acetylation which is cleared by the kidney. Systemic lupus erythromatous (SLE) like symptoms such as fever, arthralgia, pleural and pericardial inflammation can occur and is common in slow acetylators. The symptoms are dose and time dependent. Therefore, long term treatment with oral procainamide is not well-tolerated and the drug is avoided in renal failure.

Q7a. What is effective refractory period (ERP)?

Effective refractory period is the period during which a region of the cardiac tissue cannot be excited by an electrical impulse.

Qb. What are the different ways of increasing refractoriness in cardiac tissues? Mention the antiarrhythmic drugs which act by increasing the refractory period.

The different ways of increasing refractoriness in cardiac tissues are the following:

- *Delayed recovery of voltage-dependent inactivated sodium channels* prolongs the refractory period because an extra stimulus fails to generate propagated response as there is no inward sodium current. The sodium channel blockers delay the recovery process of the channels, increasing refractoriness in cardiac tissues.
- *Calcium channel blockade at nodal tissues:* SA node and AV node are slow response tissues because they are Ca^{2+}-current-dependent and exhibit time-dependent recovery. Calcium channel blockers such as verapamil and diltiazem slow the action potential upstroke in the AV nodal cells leading to slowing of conduction velocity and increase in AV nodal refractory period.
- *Prolongation of action potential duration and repolarization due to inhibition of delayed rectifier K^+ current* increases the refractory period. Drugs which block cardiac K^+ channels are used in the treatment of re-entrant arrhythmias. Dofetilide and ibutilide are pure action potential prolonging drugs and drugs such as sotalol, amiodarone, and quinidine have additional K^+ channel blocking property.
- *Vagomimetic action predominantly at AV node* due to rich innervation with vagal afferent neurons prolongs refractory period. Digoxin exerts AV nodal blocking property through its vagomimetic action and direct action on AV node.
- *Beta-adrenergic blockade action at AV node:* Increases the AV nodal refractoriness and decreases AV nodal conduction velocity.

Qc. Which group of calcium channel blockers (CCBs) is preferred in the treatment of TD with atrial fibrillation—dihydropyridine group or non-dihydropyridine group? How do these agents act as antiarrhythmic agents?

Non-dihydropyridine group of calcium channel blockers which includes verapamil and diltiazem preferentially act on calcium channels in cardiac tissues at clinically used doses and are preferred in the treatment of arrhythmias. The SA node and AV node depends on calcium current for the depolarization phase of the action potential. Calcium channel blockers slow down the action potential upstroke in the AV nodal cells leading to slowed conduction through the AV node. Due to inhibition of L type calcium current, the excitability of the SA nodal cells is suppressed.

Dihydropyridine group of calcium channel blockers such as nifedipine on the other hand preferentially block calcium channels in vascular smooth muscles and are commonly used in the treatment of hypertension. These drugs are more vasculoselective and therefore produce reflex tachycardia in response to vasodilation and fall in blood pressure, which is an undesirable effect in the setting of arrhythmia.

Q8a. Considering the clinical setting of patient TD, which drug would you choose to control the ventricular rate in atrial fibrillation experienced by the patient TD?

Patient TD is experiencing acute onset of atrial fibrillation with associated impaired left ventricular function, amiodarone or digoxin has been recommended for control of ventricular response rate because of minimal negative inotropic effect.

Hence, digoxin or amiodarone is a reasonable treatment option in patient 'TD' with evidence of heart failure (low LVEF, rales in the chest, edema in legs, congested neck veins) and characteristic features of atrial fibrillation such as rapid pulse rate of 155 beats/min, irregularly irregular pulse and lack of P wave in ECG.

Qb. Mention the contraindications if any, associated with the use of digoxin in atrial fibrillation.

Digoxin is contraindicated in conditions of high sympathetic stress such as thyrotoxicosis and post-surgery and in hypoxia due to chronic lung disease. This is because increased sympathetic activity and hypoxia can potentiate digitalis-induced changes in automaticity and delayed afterdepolarisations, thus increasing the risk of digitalis toxicity.

CASE 2: CASE OF TORSADES DE POINTES (TDP)

A 60-year-old female KY is admitted to the ICU with complaints of dizziness, confusion, shortness of breath and sweating. She is a known case of diabetes and hypertension and is controlled with medications. There was a recent history of azithromycin intake for upper respiratory tract infection. Vital signs are: HR 50 bpm, BP 130/90 mmHg, RR is 18 per minute, O_2 saturation is 98% on room air and temperature 36.8°C.

ECG showed sinus bradycardia with heart rate of 50 bpm with prolonged QT interval of 620 ms with ventricular bigeminy.

Investigations revealed electrolyte abnormalities: **Hypokalemia with a potassium of 2.6 mmol/L, hypomagnesaemia with magnesium of 1.4 mg/dl.**

Diagnosis is 'torsades de pointes' which is a polymorphic arrhythmia that can rapidly develop into ventricular fibrillation.

Qa. What is 'torsades de pointes'? Mention the causes of this type of arrhythmia. What might have led to the development of torsades de pointes in case of KY?

Torsades de pointes (TdP) is a type of polymorphic ventricular tachyarrhythmia in which the QRS complexes appear to twist around the baseline.

It may be congenital or acquired long QT syndrome. Congenital LQTS has been associated with genes coding for cardiac ion channels. The most common cause of torsades de pointes is acquired prolongation in the QT interval because of drugs. Many drugs are known to cause QT prolongation, including antipsychotics, TCAs, macrolide antibiotics and antiarrhythmic drugs (class IA, IC, and III).

In case of KY, torsades de pointes could be due to administration of azithromycin for the treatment of upper respiratory tract infection. This arrhythmia is exacerbated by the presence of other risk factors that disturb repolarization such as slow heart rates, hypokalemia, hypomagnesaemia and female sex.

Qb. How would you treat the patient KY, a case of torsades de pointes?

The treatment of torsades de pointes is as follows:

- Discontinue the causative medication
- Correct electrolyte disorders such as hypokalemia and hypomagnesaemia: Give 40 mg potassium and 2 g magnesium bolus IV with an infusion at a rate 1 g/hr to rectify electrolyte imbalance. Magnesium sulphate suppresses torsades de pointes by decreasing the influx of calcium ions which in turn results in decreased amplitude of early afterdepolarization.

- To prevent subsequent episodes, increase the heart rate until cause of TdP is corrected and/or cleared from the body. Pharmacologic pacing (using isoproterenol) or transvenous pacing may be necessary to suppress arrhythmia by increasing the baseline heart rate to 100–150 bpm since QT prolongation is more prominent in slow heart rates.
- IV lidocaine, a class IIb antiarrhythmic agent that shortens QT interval can also be used.

(Cardioversion is only indicated when patient becomes hemodynamically compromised)

Qc. How likely is amiodarone to cause torsades de pointes (TdP)?

A hallmark of class III drug is 'reverse' use dependence which means the drug binds more avidly to ion channels during slower heart rates than at rapid heart rates so action potential (AP) prolongation is most marked at slow heart rates and least marked at fast rates. Action potential prolongation results in increased refractoriness which is an effective way of treating re-entry. However, disproportionate prolongation of action potential and QT interval when underlying heart rate is slow precipitates torsades de pointes.

Of all the class III antiarrhythmic agents, amiodarone and dronedarone do not show reverse use dependence. Therefore, despite marked QT prolongation and bradycardia typical of chronic amiodarone therapy, torsades de pointes and other drug-induced arrhythmia are rare.

CASE 3: A CASE OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (PSVT)

SK, a 22-year-old adult male, presented to the OPD with complaints of palpitations and chest discomfort since morning. On examination, his pulse could not be counted. ECG revealed narrow QRS complex and absence of P wave. Heart rate was 215/min. There was no response to valsalva manoeuvre. Adenosine injection 1.3 mg was given as a rapid bolus followed by rapid saline flush. Immediately his heart rate came down to 130/min.

Qa. Given that administration of adenosine injection in patient SK reduces the heart rate from 215/min to 130/min. What is the underlying mechanism behind the therapeutic effect of adenosine in patient SK?

Adenosine acts on cardiac A1 receptors to reduce cyclic adenosine monophosphate activity which inhibits inward calcium current decreasing the pacemaker current and slowing conduction through the AV node due to increased refractoriness. This is useful in restoring the normal sinus rhythm in patients with paroxysmal supraventricular tachycardia.

Qb. Adenosine is known to induce ventricular asystole at therapeutic doses. Is this action deleterious or beneficial for the patient SK?

Adenosine induced cardiac asystole at therapeutic doses is not damaging to the heart because it lasts for less than 5 seconds. On the contrary, adenosine-induced asystole has been used to induce transient systemic hypotension for various vascular procedures.

Qc. Why is adenosine administered as a rapid bolus dose?

Adenosine is rapidly cleared from the circulation via cellular uptake through carrier-mediated transport and subsequently metabolised by adenosine deaminase resulting in an elimination half-life of <1.5 seconds in blood. So, if adenosine is slowly administered, it is eliminated from the circulation before it reaches the heart resulting in minimal therapeutic efficacy. Therefore, adenosine is administered as a rapid bolus dose so that it quickly reaches the target site and produces immediate onset of action in the management of arrhythmias.

Qd. What are the advantages of administering adenosine as a rapid bolus dose?

Adenosine administered as a rapid bolus dose has immediate onset of action and the adverse effects if any are short lived because adenosine has an extremely short half-life, less than 1.5 seconds in blood, which enables rapid spontaneous offset. The side effects arising from bolus adenosine are not generally serious and are transient because of rapid metabolism.

Qe. How can adenosine action be potentiated or inhibited? Give examples.

Dipyridamole, an adenosine uptake inhibitor, enhances adenosine action and denervated hearts (i.e. cardiac transplant patients) may be more sensitive than innervated hearts to adenosine.

Drugs such as methylxanthines block adenosine receptors and inhibit adenosine action.

CASE 4: A CASE OF WPW SYNDROME (ANATOMICALLY DEFINED RE-ENTRY)

A 45-year-old female patient MN presented to the emergency department with complaints of episodes of palpitation and chest tightness. He recalls there have been similar recurrent self-terminating episodes in the past. ECG confirms type A WPW syndrome with short PR interval, delta waves and widened QRS complex.

Qa. What do you understand by 're-entry phenomenon'? Mention the conditions necessary for a re-entrant electrical circuit to occur.

Re-entry of an electrical impulse occurs when a self-sustaining electrical circuit stimulates an area of the myocardium repeatedly and rapidly.

Two conditions must be presented for a re-entrant electrical circuit to occur:

i. Unidirectional block (anterograde conduction is prohibited, but retrograde conduction is permitted.
ii. Slowed retrograde conduction velocity

Qb. In case of MN diagnosed with Wolff-Parkinson-White (WPW) syndrome, how does re-entrant electrical circuit predispose the individual to tachyarrhythmias?

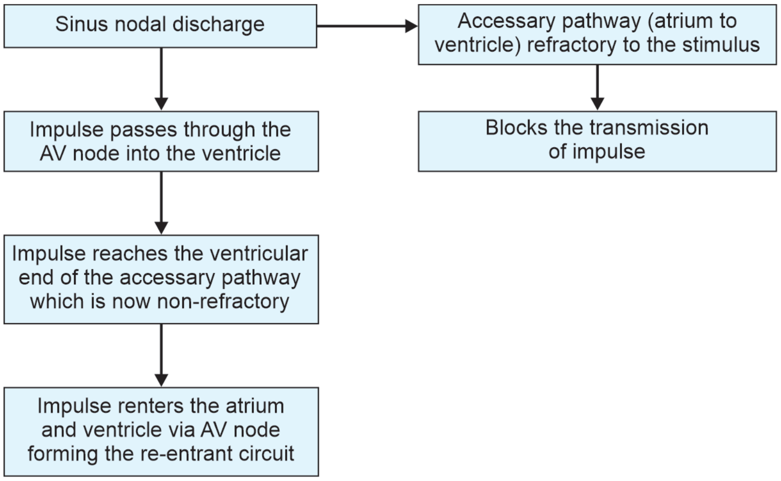

Sinus nodal discharge
Accessary pathway (atrium to ventricle) refractory to the stimulus
Impulse passes through the AV node into the ventricle
Blocks the transmission of impulse
Impulse reaches the ventricular end of the accessary pathway which is now non-refractory
Impulse renters the atrium and ventricle via AV node forming the re-entrant circuit

Fig. 7.5: Anatomically defined re-entry (e.g. WPW syndrome)

Patients with WPW syndrome have accessory connections between the atrium and the ventricle. With each sinus node depolarization the impulse can propagate via AV node or through the non-nodal accessary pathway.

It is important to note that the electrophysiologic properties of the AV node and accessary pathway are different. So, at a certain time point, while the accessary pathway is refractory to the stimulus, the AV node is non-refractory and this allows the conduction of the impulses from the atrium into the ventricle through the AV node.

Further, when the impulse reaches the ventricular end of the accessary pathway, it is no longer refractory, so the impulse passes through it, enters the atrium and then re-enters the ventricle via AV node forming a circuit. This is known as anatomically defined re-entry.

Qc. Which antiarrhythmic agents are useful in the treatment of Wolff-Parkinson-White (WPW) syndrome-associated arrhythmias?

The primary therapy for anatomically defined re-entry as in Wolff-Parkinson-White (WPW) syndrome is radiofrequency (RF) ablation. Drug therapy can be useful in some instances, such as in patients who refuse RF ablation or in patients with risk of complications.

Class Ic drugs (e.g. flecainide, propafenone) and class III antiarrhythmic medications (e.g. amiodarone, sotalol) will prolong the accessory pathway refractory period and slow down conduction velocity. This helps to extinguish the propagating re-entrant wavefront and reduce the incidence of re-entrant arrhythmias. If the patient has a history of atrial fibrillation or atrial flutter, an AV nodal blocking medication should also be used.

CASE 5: VENTRICULAR TACHYCARDIA IN ACUTE MYOCARDIAL INFARCTION

A 65-year-old woman RY presented to the ED with complaints of crushing substernal chest pain and shortness of breath that had worsened over the past several hours.

On examination, the heart rate was 210 b/min and blood pressure 110/70 mmHg. ECG revealed a wide complex tachycardia and ST-segment elevated myocardial infarction.

She received O_2 (by mask) and lidocaine (100 mg intravenously). Myocardial infarction was treated with aspirin, beta-blocker therapy and nitroglycerine. Percutaneous angioplasty was performed.

Qa. What is 'functionally defined re-entry'? Does functionally defined re-entry have a role in the genesis of ventricular arrhythmia in myocardial infarction?

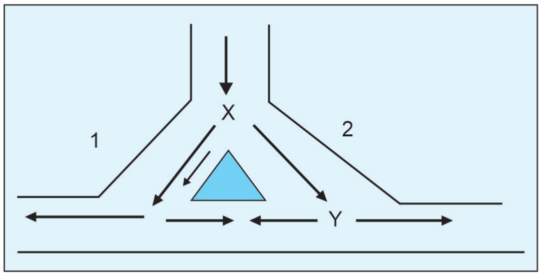
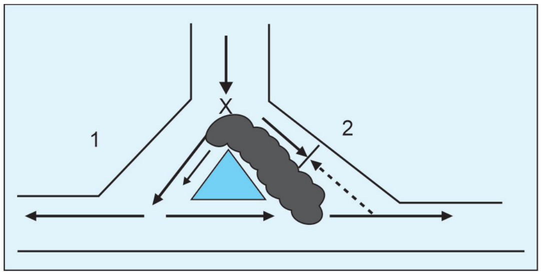


Fig. 7.6: Normal electric pathway

In normal impulse conduction, an impulse travelling down a pathway arrives at point X, where it is able to travel down two alternate pathways, 1 and 2. In the absence of re-entry, the impulses continue on and depolarize different areas of the ventricle.



Re-entrant electric pathway

Fig. 7.7: Functional re-entry in the ventricle

In functionally defined re-entry, one of the branch pathways is pathologically disrupted because the ischaemic tissue of the myocardium (pathway 2) is refractory to the stimulus. So, the impulse conducts through pathway 1, and proceeds to point Y. At this point, the ischaemic cells in pathway 2 are no more refractory and the impulse conducts in a retrograde manner, up through pathway 2 towards point X. So, the cells here will be re-excited (first by the original pathway and the other from the retrograde pathway). The circus movement of the impulse in the ventricular myocardium eventually leads to the genesis of ventricular arrhythmia.

Ventricular fibrillation (VF) following ventricular tachycardia (VT) may be described as a functionally defined re-entry problem caused by multiple mini re-entrant circuits spontaneously created within the ventricular myocardium.

Qb. Why do you think lidocaine is the first choice drug for the management of ventricular tachycardia secondary to ischaemic heart disease?

Lidocaine exhibits *use (frequency) dependence* which means that it binds more avidly to Na^+ ion channels during rapid heart rates and in ischaemic tissues which display spontaneous diastolic depolarization. In such situations, sodium channels spend more time in open and inactivated states and less time in resting states.

Lidocaine shows state-dependent block. It has high binding affinity for sodium channels in the open and/or inactivated states with very little affinity for the Na^+ channels in the resting state. Also the time taken for recovery from the channel is less than 1 second. So, it binds to the sodium channel during the depolarization phase and rapidly dissociates during the diastolic interval. Thus, the characteristic features of lidocaine makes it appropriate for use in ventricular tachycardia secondary to ischaemic heart disease.

Qc. Explain the reason why lidocaine is not effective in the treatment of atrial fibrillation.

Lidocaine is not useful in the treatment of atrial fibrillation because atrial action potentials are so short that the Na^+ channels are in the inactivated state only for a brief period compared with diastolic times, which are relatively long. The Na^+ channels spend more time in the resting state and lidocaine has more affinity to bind to the Na^+ channels in open and/or inactivated states. Therefore, atrial arrhythmias do not respond well to lidocaine.

Qd. In Cardiac Arrhythmia Suppression Trial (CAST), the mortality rates among patients with myocardial infarction treated with flecainide was 2 to 3 fold higher than those treated with placebo. How do you explain the increased mortality in such patients treated with flecainide for arrhythmia suppression?

One of the ways to treat re-entrant arrhythmias is to block action potential propagation. Sodium channel blockers such as flecainide increase the refractoriness in non-nodal tissues and may decrease the conduction velocity sufficiently to extinguish the propagating re-entrant wavefront. But conduction slowing is a critical factor in the genesis of re-entrant arrhythmias. Thus, whether a given drug exacerbates or suppresses re-entrant arrhythmias depends on the balance between its effects on refractoriness and on conduction in a particular re-entrant circuit.

Flecainide (class Ic) is a potent sodium channel blocker and has a very long T recovery of greater than 10 seconds. So, because of high binding affinity for the sodium channels and slow rate of dissociation from the channels, it markedly slows down phase 0 fast depolarization and significantly slows down conduction in the myocardial tissue. If the impulse is not completely abolished, then drug-induced slowing can actually promote re-entry arrhythmia. The 'surviving' impulse may use the original re-entrant pathway to propagate the arrhythmia, or it may find other pathways and create new re-entrant circuits. This can result in fatal re-entrant tacharrhythmias and increased mortality in patients convalescing from myocardial infarction.

Qe. Is lidocaine useful in the treatment of digitalis-induced ventricular arrhythmias? If yes, mention the route of administration of lidocaine for the treatment of ventricular arrhythmias.

Lidocaine is the drug of choice for the treatment of ventricular arrhythmias arising from digitalis intoxication. Lidocaine is administered intravenously for the treatment of arrhythmias and the onset of action is immediate (45 to 90 seconds). It is not given orally because it has high first pass metabolism and is destroyed before it reaches the systemic circulation.

Qf. What is the first sign of toxicity with lidocaine therapy? What are the signs and symptoms of lidocaine toxicity at higher doses?

Lidocaine acts primarily on the central nervous system (CNS) and cardiovascular system (CVS) by binding to the voltage-gated sodium channels and inhibiting the propagation of action potential. Since the CNS is more sensitive to electrophysiological changes than the CVS, neurological symptoms such as dizziness, tinnitus, nystagmus, speech changes and perioral numbness usually precede cardiovascular effects and are the early signs of toxicity.

A moderate-to-severe overdose results in generalized tonic-clonic seizures, followed by central nervous system depression along with a depressed cardiovascular status including blood pressure, heart and respiratory rates, disorientation, drowsiness and loss of consciousness.

Qg. To which class of antiarrhythmic drug does mexiletine belong to? What is the advantage of mexiletine over lidocaine? What are the likely side effects associated with mexiletine use in the chronic treatment of arrhythmia?

Like lidocaine, mexiletine is classified as sodium channel blocker class IIb.

Mexiletine is a modified lidocaine and has an advantage over lidocaine in that it can be given orally with longer-lasting effects. It is indicated for the chronic treatment of ventricular arrhythmias associated with previous myocardial infarction.

Tremor is early sign of mexiletine toxicity. Hypotension, bradycardia, widened QRS, dizziness and nystagmus may occur.

Qh. The clinical data of RY suggests that she was treated with beta-blocker after acute myocardial infarction. Mention the beneficial effects of therapy with beta-blocker in myocardial infarction.

Beta-blockers via reduction in heart rate and blood pressure reduce myocardial workload, and thus oxygen demand. This helps to reduce myocardial ischaemia, limit infarct size, and may prevent the development of definite infarction in acute coronary syndrome patients.

Early use of beta-blockers in acute myocardial infarction has been shown to reduce the incidence of supraventricular and malignant ventricular arrhythmias, reduce the use of other antiarrhythmic medications, decrease chest pain symptoms, decrease sudden cardiac death, and early and late infarction.

Qi. Mention the coexisting conditions with arrhythmia in which β-blockers are contraindicated.

Beta-blockers are contraindicated in patients with asthma, symptomatic hypotension or bradycardia and severe decompensated heart failure. Blood glucose levels should be closely monitored in diabetic patients on treatment with beta-blockers as beta-blockers mask symptoms of hypoglycaemia.

In patients with bronchial asthma and chronic obstructive pulmonary disease non-dihydropyridine calcium channel blockers are preferred.

Qj. Explain why β-blocker alone should not be used to treat arrhythmias associated with conditions such as pheochromocytoma, thyrotoxicosis and clonidine withdrawal.

Arrhythmias due to conditions such as pheochromocytoma, thyrotoxicosis and clonidine withdrawal are associated with high sympathetic stress. Use of a beta-blocker alone can result in unopposed α-adrenergic stimulation, resulting in severe hypertension and/or α-adrenergic-mediated arrhythmias. Therefore, in such cases, arrhythmias should be treated with both α- and β-blockers or a drug having α-and β-blocking property such as labetalol.

Case Continued

One year later Mrs RY once again arrived in the emergency department with ventricular tachycardia. Therapy was initiated with amiodarone infused rapidly over the first 10 minutes followed by slow infusion. After an adequate response was seen there was a changeover to oral therapy which was initiated at the loading dose (i.e. 200 mg three times a day).

Qa. Why is amiodarone administered as a loading dose?

Amiodarone is a highly lipophilic drug and is extensively distributed into tissues particularly, the adipose tissue and skeletal muscle. It has a long half-life (35 to 110 days) and requires months for blood levels to reach equilibrium for optimal therapeutic effect. Hence, loading doses are used to achieve the plasma concentration quickly.

Qb. Why is amiodarone known as broad spectrum antiarrhythmic agent?

Amiodarone is known as broad spectrum antiarrhythmic agent as it is one of the most commonly used drug to suppress *supraventricular and ventricular arrhythmias.* It is mainly a class III antiarrhythmic agent, but it also acts as a class I, class II, and class IV antiarrhythmic.

Amiodarone exerts its antiarrhythmic effect primarily via *blockade of voltage-gated potassium channels* and causes prolongation of repolarization of cardiac action potential duration reducing the incidence of re-entry arrhythmias. As a class I agent, amiodarone blocks Na^+ channels and thereby decreases altered automaticity in pacemaker cells. It exerts class II antiarrhytmic activity, by non-competitively antagonizing α- and β-adrenergic receptors. Finally, as a Ca^{2+} channel blocker (class IV), amiodarone can suppress conduction velocity and discharge in the AV node and SA node. Long-term amiodarone therapy is commonly used for the maintenance of sinus rhythm for patients with paroxysmal atrial fibrillation.

Qc. What are the adverse effects of long-term amiodarone therapy in the management of arrhythmias?

Amiodarone has many serious adverse effects involving different organ systems.

1. Either hypothyroidism or hyperthyroidism can result from dysregulation of thyroid hormone metabolism.
2. Liver toxicity can range from an asymptomatic elevation of transaminases to fulminant hepatitis.
3. Pneumonitis leading to pulmonary fibrosis is a dreaded complication of amiodarone.
4. Central nervous system effects include ataxia, tremor, dizziness and peripheral neuropathy.
5. Photosensitivity skin reactions and corneal deposits in the eye can occur.
6. Amiodarone is metabolised by cytochrome P450 enzyme system and hence clinically significant drug–drug interactions are common with drugs involving cytochrome P450.

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Section

IV

Endocrine and Metabolic Disorders

8. Insulin and Oral Antidiabetic Drugs
9. Antithyroid Drugs and Thyroid Hormones
10. Drugs for Osteoporosis
11. Corticosteroids

Chapter

8

Insulin and Oral Antidiabetic Drugs

CASE 1: THERAPY FOR NEWLY DETECTED DIABETES MELLITUS

WX, a 40-year-old obese female, presented with symptoms of weakness, lethargy, frequency of urination and investigations with fasting blood glucose of 187 mg/dl HbA1C 8.5%, postprandial glucose (PG) 280 mg/dl, and this was repeated several times with similar results. She underwent a diet and exercise program, but after 6 months was able to decrease her weight only from 127 to 118 kg. There was no significant change in her fasting serum glucose levels. Her fasting cholesterol level was 290 mg/dl, with a low density lipoprotein (LDL) 190 mg/dl and HDL 30 mg/dl. Her renal and hepatic functions are within normal limits. Her blood pressure is within normal limits. There is a family history of diabetes.

Qa. Mention the criteria recommended by the expert committee of the American Diabetes Association (ADA) for diagnosing a patient with diabetes.

The expert committee of the ADA has established the diagnostic criteria for diabetes for non-pregnant individuals of any age which is as follows:

- FPG >126 mg/dl (7.0 mmol/L) OR
- 2-h PG >200 mg/dl (11.1 mmol/L) during oral glucose tolerance test (OGTT) OR
- HbA1C > 6.5% (48 mmol/mol) OR
- In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose >200 mg/dl (11.1 mmol/L).

Qb. How would you confirm diabetes mellitus in WX from the clinical presentation and investigation results?

WX, an obese female, with family history of diabetes has symptoms of diabetes such as frequency in urination and fatigue. The laboratory values (HbA1C: 8.5%, FPG: 187 mg/dl, PG: 280 mg/dl) are not within normal limits. As per the diagnostic criteria laid down by the American Diabetes Association (ADA), WX is diagnosed as a case of type 2 diabetes mellitus.

Qc. What are the patient's specific and drug-specific factors taken into consideration while selecting a drug class in the management of type 2 diabetes mellitus?

A patient-centered approach should be used to guide the choice of pharmacologic agents. The considerations include efficacy, safety, age, body weight, extraglycaemic benefits (cardiovascular outcome, renal outcome, etc.), injection burden, cost and accompanying illness.

Qd. The physician decides to initiate an oral hypoglycaemic agent for WX. What are the available oral hypoglycaemic drugs for the management of type 2 diabetes mellitus?

Sulfonylureas	1st Generation: Tolbutamide, chlorpropamide 2nd Generation: Gilbenclamide, glipizide, gliclazide, glimepiride
Meglitinide analogues	Repaglinide, nateglinide
Biguanides	Phenformin, metformin
α-Glucosidase inhibitors	Acarbose, voglibose
Thiazolidinediones (glitazones)	Pioglitazones, rosiglitazones
Incretin mimetics	
DPP-IV inhibitors	Vildagliptin, sitagliptin
GLP-1 agonists	Exenatide, liraglutide
Sodium–glucose cotransporter inhibitors (SGLT-2)	Canagliflozin, dapagliflozin

Qe. Which oral antidiabetic agent would you prefer in case of WX, who is newly diagnosed with diabetes? Justify your selection of the drug.

Metformin is a biguanide compound which is antihyperglycaemic, reduces insulin resistance and has cardioprotective effects.

Metformin has a weight neutral/weight lowering effect, reduces hypertriglyceridaemia, total cholesterol and improves HDL-C level. It has a favourable effect on clotting factors, platelet function and vascular function. Since metformin does not directly stimulate insulin secretion, hypoglycaemia risk may be lower than for that of other oral antidiabetes drugs.

Metformin has been shown to cause a reduction in all cause mortality and vascular complications independent of glycaemic control. It is the first line therapy in the management of obese insulin resistant type 2 diabetes and in the prevention of vascular complications.

Qf. Why is sulfonylurea, an oral hypoglycaemic agent, not used as first choice drug in case of WX?

Sulfonylurea use is associated with weight gain and hence preferred for the treatment of underweight diabetic patient. Studies have suggested that sulfonylurea use may elevate the risk of cardiovascular disease and increase mortality among patients with diabetes.

Sulfonylureas should be considered for diabetic patients who are not overweight or those for whom metformin is contraindicated or is not enough to achieve adequate glycaemic control. WX is obese with body weight of 118 kg and has abnormal lipid profile with cardiovascular risks. Therefore, metformin is preferred over sulfonylurea as the first-line choice for the treatment of diabetes in WX.

Qg. What are the underlying molecular mechanisms through which metformin regulates glucose and lipid metabolism?

Metformin acts by lowering blood glucose and lipids in the following ways:

- Suppresses hepatic glucose production through inhibition of hepatic gluconeogenesis through activation of AMP kinase enzyme.

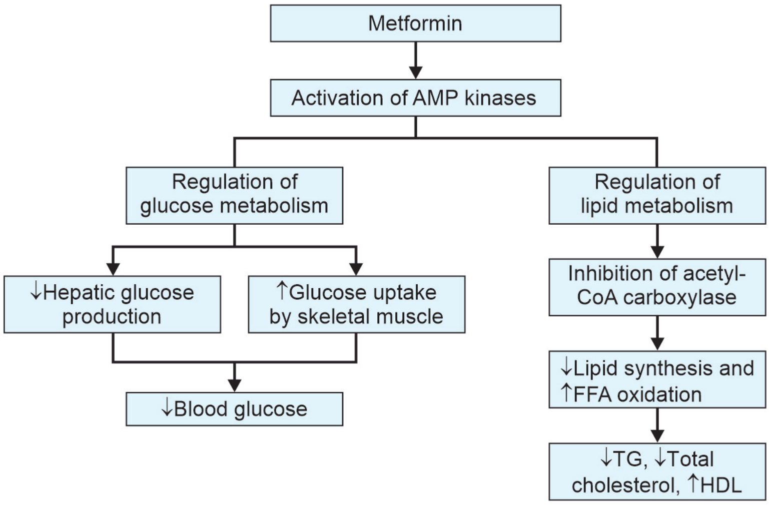

Metformin
Activation of AMP kinases
Regulation of glucose metabolism
Regulation of lipid metabolism
↓Hepatic glucose production
↑Glucose uptake by skeletal muscle
↓Blood glucose
Inhibition of acetyl-CoA carboxylase
↓Lipid synthesis and ↑FFA oxidation
↓TG, ↓Total cholesterol, ↑HDL

Fig. 8.1: Metformin: Regulation of glucose and lipid metabolism

- Stimulates insulin-mediated peripheral uptake of glucose in tissues
- Inhibits glucose absorption from the intestine
- Stimulates glycolysis in the tissues
- Reduces plasma glucagon levels
- Decreases appetite
- Decreases triglycerides and LDL-C and increases HDL-C through decreased activity and expression of acetyl-CoA carboxylase contributing to decreased lipid synthesis and increased fatty acid oxidation.

CASE 2: SULFONYLUREA THERAPY IN TYPE 2 DIABETES MELLITUS

A 74-year-old man KV, is found by his family to be disoriented and confused. In the emergency room he is found to be hypoglycaemic. He is afebrile but his physical examination is otherwise normal. A bolus of intravenous dextrose is administered and the patient quickly recovers. His glucose is 122 mg/dl and his neurologic examination had returned to baseline. Further history reveals that the patient has type 2 diabetes mellitus for which he takes glimepiride 4 mg OD. He also has a history of congestive heart failure for which he was hospitalized three times last year. His serum creatinine was 1.6 mg/dl when last investigated.

Qa. Why hypoglycaemia is common in patients with diabetes but not in normal individuals?

In people without diabetes, fall in blood glucose concentration to less than 70 mg/dl is followed by activation of compensatory mechanisms of the body, releasing glucagon, epinephrine, cortisone and growth hormones which raise the plasma glucose levels back towards normal by increasing hepatic glucose output.

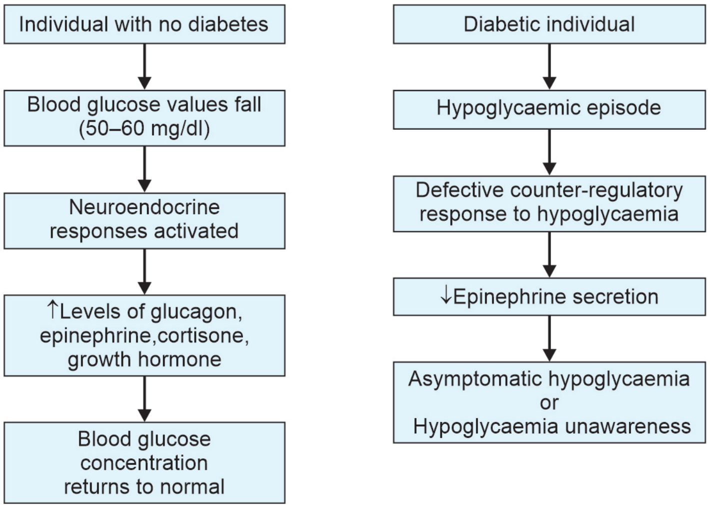

Individual with no diabetes
Blood glucose values fall (50–60 mg/dl)
Neuroendocrine responses activated
↑Levels of glucagon, epinephrine,cortisone, growth hormone
Blood glucose concentration returns to normal
Diabetic individual
Hypoglycaemic episode
Defective counter-regulatory response to hypoglycaemia
↓Epinephrine secretion
Asymptomatic hypoglycaemia
or
Hypoglycaemia unawareness

Fig. 8.2: Effects of hypoglycaemia in diabetic and non-diabetic individual

In people with diabetes, the counter-regulatory hormonal response to hypoglycaemia is defective, resulting in failure to recover the blood glucose to normal. Certain circumstances further predispose patients to hypoglycaemic unawareness or severe hypoglycaemia. These include medications such as β-blockers, intensive insulin therapy, skipped meals or inadequate carbohydrate intake and excessive alcohol intake.

Qb. What are the warning signs and symptoms of hypoglycaemia?

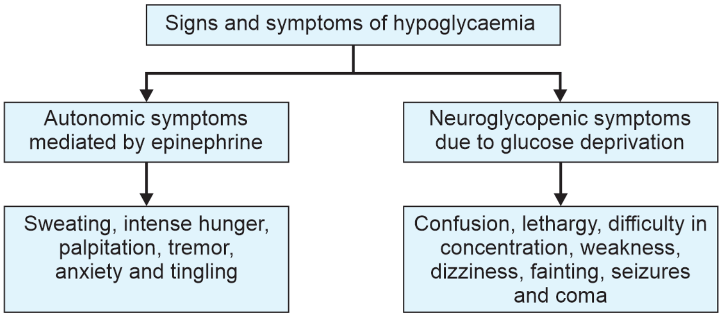

Signs and symptoms of hypoglycaemia
Autonomic symptoms mediated by epinephrine
Neuroglycopenic symptoms due to glucose deprivation
Sweating, intense hunger, palpitation, tremor, anxiety and tingling
Confusion, lethargy, difficulty in concentration, weakness, dizziness, fainting, seizures and coma

Fig. 8.3: Signs and symptoms of hypoglycaemia

Symptoms of hypoglycaemia are categorized into autonomic and neuroglycopenic.

Autonomic symptoms are thought to be mediated by epinephrine and include sweating, intense hunger, palpitations, tremor, tingling, and anxiety.

Neuroglycopenic symptoms resulting from neuronal fuel deprivation (glucose) include difficulty in concentrating, lethargy, confusion, agitation, weakness, and possibly, slurred speech, dizziness, and fainting. Profound behavioural changes, seizures, and coma are more severe manifestations of neuroglycopenia. Prolonged, severe neuroglycopenia ultimately results in death.

Qc. What are the glucose lowering mechanisms of glimepiride, a sulfonylurea, in the management of diabetes?

Glimepiride acts as an oral hypoglycaemic agent, mainly by stimulation of insulin secretion by pancreatic β cells. It binds and closes ATP sensitive K^+ channel on the cell membrane of pancreatic β cells, preventing the outflow of potassium ions thereby causing depolarization of the cell membrane. This depolarization opens voltage-gated Ca^{2+} channels causing a rise in intracellular calcium which in turn leads to increased fusion of insulin granules with the cell membrane, resulting in the release of large amounts of insulin which in turn increases glucose utilization by the peripheral tissues.

Qd. What are the likely reasons for sulfonylurea-induced hypoglycaemia considering the case of KV?

The biological effect of sulfonylureas often lasts longer than their plasma half-life because of strong drug receptor interactions and formation of active metabolites persisting 24 hours or more. Moreover, their half-life is prolonged in the presence of renal failure.

In an elderly patient as in case of KV, a number of factors predispose to hypoglycaemia including polypharmacy, intercurrent illness and declining renal and hepatic function. In these patients, autonomic failure secondary to aging and longer duration of diabetes, is responsible for asymptomatic and occult hypoglycaemia.

Qe. What precautions should be taken to reduce the incidence of hypoglycaemia related to sulfonylurea use in a diabetic patient?

1. Sulfonylureas should be used with caution in patients who are undernourished or alcohol abusers, in patients with impaired renal or cardiac function or gastrointestinal disease.
2. Patients should be educated about those situations in which hypoglycaemia is most likely to occur: After exercise or a missed meal or when taking an excessive dosage.
3. Glipizide is metabolized by the liver into several inactive metabolites, and its clearance and elimination half-life are not affected by reduction in the estimated GFR, so dose adjustments are not necessary in patients with chronic kidney disease. Therefore, *glipizide is the sulfonylurea of choice in patients with CKD.*
4. Even though, the risk of hypoglycaemia is lower with the newer sulfonylureas (glipizide, gliclazide and glimiperide), these episodes are more frequent and dangerous in elderly. Regular blood glucose monitoring is therefore necessary.

Qf. How would you compare the effects of meglitinides (non-sulfonylurea insulin secretagogues) with sulfonylurea in the treatment of diabetes?

Meglitinides act by stimulating insulin secretion from the pancreatic β cells, acting on the ATP sensitive K^+ channels. The mechanism of action is similar to sulfonylureas but unlike sulfonylureas, they have *a rapid onset and shorter duration of action, so they are given with meals to enhance postprandial glucose utilization.* The release of insulin depends on the glucose level and decreases at low concentrations of glucose. So the chances of hypoglycaemia is less.

Qg. How does presence of chronic kidney disease (CKD) influence the use of oral antidiabetic medications in a patient suffering from diabetes?

Drug class	*Use of antihyperglycaemic agents in chronic kidney disease (CKD)*
Sulfonylureas	• Hypoglycaemia is a primary treatment concern in chronic kidney disease (CKD) patients • Glipizide is the sulfonylurea of choice in CKD patients as it is metabolized by the liver into inactive metabolites
Metformin	• Metformin may be safely used in patients with mild-to-moderate 'renal impairment' • Metformin is contraindicated in patients with an eGFR <30 ml/min/1.73 m^2

Contd.

Drug class	*Use of antihyperglycaemic agents in chronic kidney disease (CKD)*
Glitazones	• Avoided due to concerns of refractory fluid retention, higher BP, congestive heart failure, and increased fracture risk
DPP IV inhibitors	• Dipeptidyl peptidase-4 (DPP-4) inhibitors are labelled for use in CKD, but sitagliptin, saxagliptin, and alogliptin require downward dose titration on the basis of eGFR
GLP-I analogues	• Protection against chronic kidney disease progression in patients with T2DM and CKD stages 3 and 4
SGLT2 inhibitor	• Renoprotective action showing reduction in albuminuria and reduce the progression of kidney disease
Insulin	• Insulin therapy is a mainstay of therapy in patients with CKD-insulin doses are individualized on the basis of each patient's glycaemic response and patterns

Qh. KV was instructed to avoid consuming alcohol after ingestion of sulfonylureas. Explain why.

Sulfonylureas particularly chlorpropamide and tolbutamide through inhibition of aldehyde dehydrogenase, an enzyme involved in the metabolism of alcohol into non-toxic acetate, leads to accumulation of acetyldehyde, which is a highly toxic substance responsible for symptoms of flushing and palpitation. This is known as *'disulfiram reaction'*. Therefore, the patient should be instructed to avoid taking alcohol with sulfonylureas.

Qi. If KV develops hyponatremia while on sulfonylurea treatment, what could be the possible reason for sulfonylurea-induced hyponatremia?

Sulfonylureas can cause hyponatremia by potentiating the renal effects of antidiuretic hormone, identical with that of inappropriate secretion of ADH. This inappropriate ADH activity causes *dilutional hyponatremia associated with increased renal water retention* and commonly occurs at therapeutic doses of chlorpropamide or tolbutamide.

CASE 3: TRIPLE DRUG THERAPY IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

LS, a 54-year-old obese woman with BMI 36.4, 8–10 year history of type 2 DM has Hb1Ac 9.5% on laboratory testing. Her current antihyperglycaemic medications are metformin 1000 mg BD, and gliclazide 120 mg. There is history of hypertension, dyslipidaemia and obesity (BMI 32.6 kg/m^2) and she is on treatment with medications for the same.

Treatment advised: Tab. sitagliptin 100 mg once a day is added to metformin 1000 mg BD, and gliclazide 120 mg to improve glycaemic control.

Qa. What could be the possible reasons for not including pioglitazone as the third drug in the treatment regimen of the patient LS to achieve adequate glycaemic target?

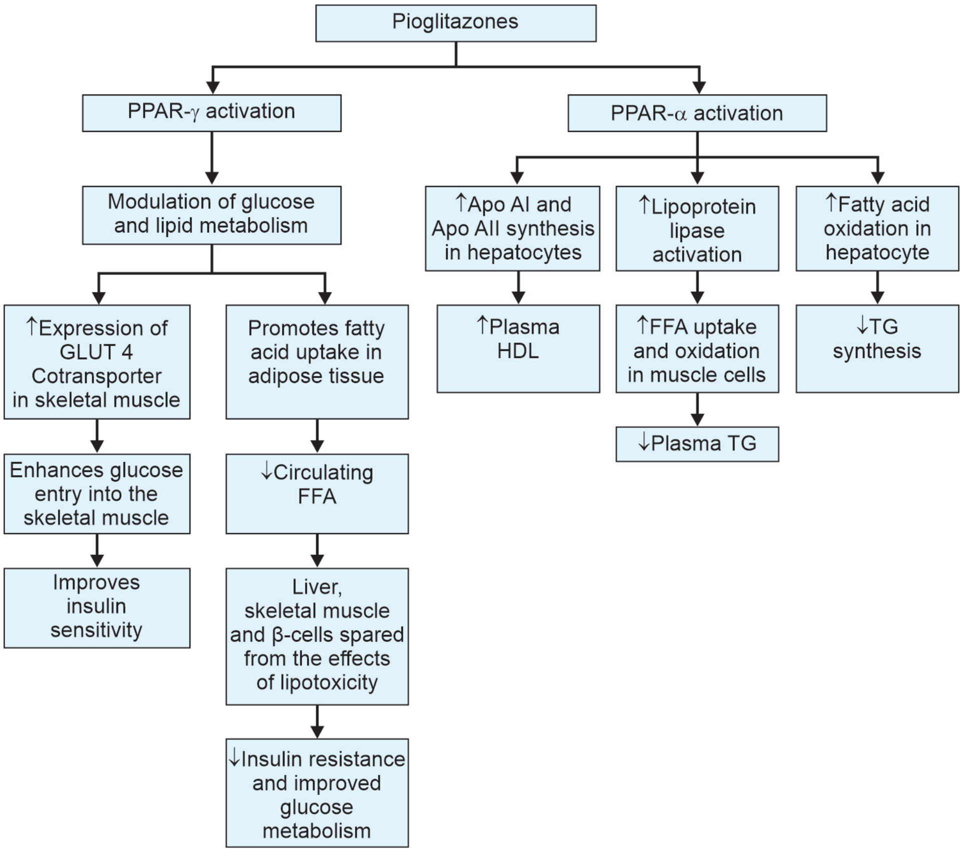
The reasons for not including pioglitazone in the treatment regimen of LS, for achieving the glycaemic target are the following:

1. Pioglitazone, a thiazolidinediones (TZD) is less preferred in obese patients because dose-related weight gain may occur due to fluid retention and fat accumulation.
2. FDA has issued black box warning regarding the association of TZD use with increased risk of developing or exacerbating heart failure. Caution is advised when used with insulin because weight gain, hypoglycaemia and fluid retention pose problems in certain patients.

3. Fluid retention with glitazones appears to be the cause of macular edema and the patient has to be referred to the ophthalmologist if there are changes in vision.
4. Pioglitazone is associated with an increased risk of bladder cancer which limits its long-term use in diabetes and is avoided in patients with history of bladder cancer.
5. Patients with osteoporosis or at risk for bone fractures (e.g. chronic steroid use) should not use TZD because of the likelihood for distal bone fractures.
6. Pioglitazone induces CYP3A4 enzyme which decreases the effectiveness of drugs metabolized by the same enzyme.
7. TZDs have not been definitely shown to reduce cardiovascular events in patients, in spite of beneficial effects on markers of cardiovascular risk.

Qb. Explain the molecular mechanisms through which glucose and lipid metabolism are regulated with pioglitazone, a thiazolidinediones (TZD) in type 2 diabetes mellitus patient.

Thiazolidinediones (TZDs) bind and activate nuclear receptor [peroxisome proliferator-activated receptor-γ (PPAR-γ)], which is expressed in many insulin sensitive tissues, including adipose (major site), skeletal muscle, and liver tissue. PPAR-γ regulates transcription of genes that influence glucose and lipid metabolism.


Pioglitazones
PPAR-γ activation
PPAR-α activation
Modulation of glucose and lipid metabolism
↑Apo AI and Apo AII synthesis in hepatocytes
↑Lipoprotein lipase activation
↑Fatty acid oxidation in hepatocyte
↑Expression of GLUT 4 Cotransporter in skeletal muscle
Promotes fatty acid uptake in adipose tissue
↑Plasma HDL
↑FFA uptake and oxidation in muscle cells
↓TG synthesis
↓Plasma TG
Enhances glucose entry into the skeletal muscle
↓Circulating FFA
Improves insulin sensitivity
Liver, skeletal muscle and β-cells spared from the effects of lipotoxicity
↓Insulin resistance and improved glucose metabolism

FFA: Free fatty acid; Apo: Apoprotein; TG: Triglyceride; HDL: High-density lipoprotein; GLUT: Glucose transporter

Fig. 8.4: Mechanism of action of pioglitazone (thiazolidinediones)

PPAR-γ stimulation increases the expression of GLUT-4, a glucose transporter that is principally responsible for insulin-stimulated glucose uptake into muscle and adipose cells. Reduced expression of GLUT-4 may contribute to the development of insulin resistance.

TZDs alter the expression of genes involved in lipid metabolism and promote fatty acid uptake and storage in adipose tissue. Because lipolysis and levels of circulating FFAs are reduced by PPAR-γ activation, other insulin-sensitive tissues such as liver, skeletal muscle and possibly pancreatic β-cells are spared from the harmful metabolic effects of high concentration of FFAs that induce insulin resistance.

PPAR-α activation increases hepatic synthesis of Apo AI and AII which leads to increased plasma HDL-cholesterol concentrations. There is increased lipoprotein lipase expression causing increased fatty acid uptake in muscle cells and hepatocytes. These metabolic changes decrease plasma triglyceride concentration and increased plasma HDL concentration.

Qc. The physician added sitagliptin to the treatment regimen of LS which is a DPP-4 inhibitor. How do DPP-4 inhibitors play a role in lowering blood glucose levels in a diabetic patient?

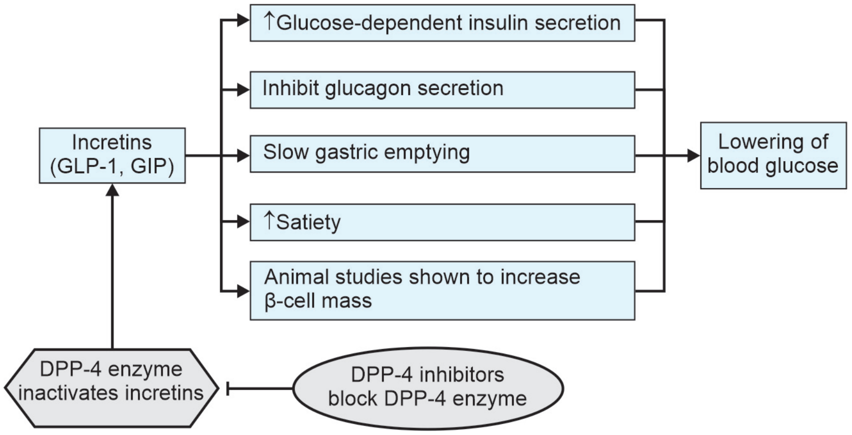

↑Glucose-dependent insulin secretion
Inhibit glucagon secretion
Incretins (GLP-1, GIP)
Slow gastric emptying
Lowering of blood glucose
↑Satiety
Animal studies shown to increase β-cell mass
DPP-4 enzyme inactivates incretins
DPP-4 inhibitors block DPP-4 enzyme

Fig. 8.5: Blood glucose lowering mechanisms of DPP-4 inhibitors

DPP-4 inhibitors by blocking DPP-4 enzyme increase incretin levels (GLP-1 and GIP) which inhibit glucagon release, increase insulin secretion, decrease gastric emptying and decrease appetite by improving satiety. Animal studies have shown to increase pancreatic beta-cell mass. All of these mechanisms acting together lower blood glucose levels.

CASE 4: LIRAGLUTIDE, GLP-1 ANALOGUE FOR THE MANAGEMENT OF DIABETES

PQ, a 55-year-old obese female, weight 92 kgs, with 5 year history of T2DM, hypertension for 10 years. Blood glucose investigations revealed RBS: 320 mg/dl and HbA1C: 8.5. She was on treatment with metformin 500 mg BD for diabetes.

Therapy was initiated with inj. liraglutide (GLP-1 analogue) with a dose of 0.6 mg subcutaneously once daily for one week, titrated upward to 1.2 mg subcutaneously once a day one week later.

PQ responds well to treatment. Her blood glucose concentration stabilzes over a period of months and the HbA1c is reduced to 6.2.

Qa. The intensification of antihyperglycaemic therapy for the patient PQ is done by adding liraglutide (GLP-1 analogue) to metformin. Justify the selection of liraglutide in this patient.

- Liraglutide is chosen for intensifying antihyperglycaemic therapy among diabetic patients who are obese with metabolic syndrome and increased risk of cardiovascular events.
- Liraglutide provides good glycaemic control, minimizes the risk of hypoglycaemia and glycaemic variability, reduces weight, suppresses appetite and minimizes weight gain, controls cardiovascular risks and improves cardiovascular outcome.

Qb. What is the expected adverse effect if liraglutide (GLP-1 analogue) is combined with sulfonylureas?

When liraglutide is combined with an insulin secretagogue such as sulfonylurea, there is increased risk of hypoglycaemia because of the synergistic action between the two drugs administered concurrently. Dose reduction of insulin secretagogue may be considered.

Qc. How does liraglutide enhance the action of GLP-1, for lowering blood glucose levels in the management of diabetes?

Liraglutide's prolonged action and long half-life of 11–15 hours are attributed to the attachment of the fatty acid (palmitic acid) to GLP-1 that reversibly binds to albumin. Albumin binding protects liraglutide from immediate degradation and elimination and cause GLP-1 to be released from albumin in a slow and consistent manner.

Qd. Why is liraglutide initially started at a low dose for one week and then titrated upwards to its therapeutic effective dose?

Liraglutide is associated with dose-dependent severe gastrointestinal side effects. To minimize the occurrence of gastrointestinal problems, it is initiated at a low dose with a gradual increase in dose.

Qe. What are the contraindications to the use of liraglutide (GLP-1 receptor agonist) in type 2 DM patient? Mention the conditions in which caution needs to be exercised with use of liraglutide.

Contraindications to use of GLP-1 receptor agonist	*Exercise caution*
• Pregnancy/lactation • DKA • Pancreatitis • Medullary thyroid cancer (MTC) and family history of MTC • MEN-type 2 • Hypersensitivity to the drug	• Moderate-to-severe renal impairment • Severe diabetic gastroparesis • Gastrointestinal disease

CASE 5: BASAL-BOLUS INSULIN THERAPY

PQ was maintained on inj. liraglutide (GLP-1 analogue) and metformin for 3 years. Recently, she visited the clinic for the follow-up of her uncontrolled blood sugars. She admitted that her physical activity was reduced and she was unable to walk because of osteoarthritis. Her HbA1c is 9.1.

After discussing various treatment options with the physician, PQ agreed to be initiated treatment with insulin glargine U-100 at 20 units every morning and metformin to be continued. The patient was instructed to increase the dose of insulin by 1 unit every day until her morning glucose was reduced to 120 mg/dl.

After 3 months into this treatment regimen, morning glucose readings were less than 120 mg/dl at 40 units of insulin glargine but her postprandial blood glucose values post afternoon meal is usually high, greater than 200 mg/dl.

The treatment regimen was modified by adding 20 units of insulin aspart prior to her afternoon meals and insulin glargine was continued. Metformin was discontinued.

Qa. Given that PQ wishes to switch over to insulin therapy, what are the available insulin preparations for the management of diabetes?

The various insulin preparations available are short-acting insulins, long-acting insulins and insulin combinations.

Insulin preparation	*Onset of action*	*Peak*	*Duration of action*
Short-acting			
Lispro	<15 min	1–2 hours	3–6 hours
Aspart	<15 min	1–2 hours	3–6 hours
Glulisine	<15 min	1–2 hours	3–6 hours
Regular	30–60 min	2–4 hours	6–10 hours
Long-acting			
Human NPH	24 hours	4–5 hours	10–18 hours
Glargine	1–2 hours	Usually no peak	Up to 24 hours
Detemir	1–2 hours	Usually no peak	Up to 24 hours
Insulin combinations			
75/25, 75% protamine lispro, 25% lispro	<15 min	1.5 hours	Up to 10–16 hours
70/30, 70% protamine aspart, 50% aspart	<15 min	1.5 hours	Up to 10–16 hours
50/50, 50% protamine lispro, 50% lispro	<15 min	1.5 hours	Up to 10–16 hours
70/30, 70% NPH, 30% regular	30–60 min	Dual	10–16

Qb. PQ was treated with basal bolus insulin therapy by combining insulin glargine (basal insulin) with insulin aspart (bolus insulin). Explain what is basal bolus insulin therapy. Which are the insulins that are used for basal therapy and for bolus therapy?

In the non-diabetic individual, the pancreas secretes boluses of insulin in response to food. Between meals and throughout the night, the pancreas secretes small amounts of insulin that are sufficient to supply energy to the cells while maintaining the blood glucose levels at consistent levels, this is known as basal insulin.

The treatment strategies used by the clinicians is to simulate the physiological pancreatic release of insulin in the management of diabetes. Bolus insulin is specifically taken at meal times for postprandial glucose utilization. Thus, short-acting or rapid-acting insulins are used. Basal insulins need to act over a relatively long period of time and therefore basal insulin will be long acting insulin.

Long acting basal insulins include NPH, glargine, detemir and degludec. Bolus doses of short-acting insulins (insulin lispro, insulin aspart, insulin glulisine) or regular insulins are given at mealtime.

Qc. What is the alternative to basal bolus insulin therapy?

Insulin pump therapy (previously referred to as continuous subcutaneous infusion of insulin) is the alternative to basal bolus insulin therapy.

Qd. What accounts for the prolonged action of insulin glargine and insulin NPH?

Insulin glargine is available as a clear solution with a pH of 4.0, *precipitates at physiologic pH, forming a depot that releases insulin slowly for up to 24 hours.* This results in delayed absorption and a less pronounced peak compared with NPH insulin.

NPH refers to N for neutral, P for protamine and H for its creator scientist name 'Hans Christian Hagedorn'. NPH insulin is obtained from the precipitation of recombinant synthesized human insulin in the presence of protamine. This process occurs in *neutral pH* with an *insulin and protamine ratio of 5:1*. The solvent from NPH insulin suspension diffuses into the subcutaneous tissue. These insulin crystals are stacked up like a heap at the injection depot and dissolve gradually leading to the protracted action of insulin.

Qe. What are the metabolic actions of insulin glargine administered to a diabetic patient such as PQ?

Insulin glargine is categorized as a long-acting insulin and has the following metabolic actions:

- It helps increase cellular intake of glucose in the liver, adipose tissue and skeletal muscles.
- It acts as basal insulin and stimulates the liver to promote hepatic glycogen synthesis, fatty acid metabolism for lipoprotein synthesis.
- In skeletal muscle, it promotes glycogen and protein synthesis.
- In adipose tissue, it helps in triglyceride synthesis and regulates lipolysis by inhibiting triglyceride hydrolysis.
- At the cellular level, it makes cell membrane permeable for ions such as potassium, magnesium, and phosphorus and increases their cellular uptake.

Qf. What could be the reasons for choosing insulin glargine over insulin NPH for basal insulin therapy?

Insulin glargine controls blood sugars in between meals and overnight. It has smooth time action profile with no peak and acts for a period up to 24 hours. Hypoglycaemia is less frequent compared to NPH. There is minimal weight gain.

Patients may show a variable pattern of response to NPH insulin with time and experience fluctuations in blood glucose levels giving rise to hypoglycaemia. Up to 80% of these day-to-day fluctuations in blood glucose responses can be accounted for by variation in the absorption of NPH insulin.

CASE 6: 'SOMOGYI PHENOMENON' AND 'DAWN PHENOMENON'

PQ managed to control her blood sugars well with insulin glargine (basal insulin) and insulin aspart (bolus insulin) and regularly monitors her blood glucose levels. One morning the fasting blood glucose readings were high. She mentioned that she had skipped dinner last night. On consulting the physician, he explained that the morning hyperglycaemia could be due to Somogyi effect and advised to take the blood glucose readings at midnight 3 am so that nocturnal hypoglycaemia is ruled out.

Qa. What is 'Somogyi phenomenon' and how is it different from 'Dawn phenomenon'?

Somogyi effect is rebound hyperglycaemiawhich occurs in response to nocturnal hypoglycaemia. It usually happens when a diabetic patient takes too much insulin before going to bed or when bedtime snack is skipped. This results in nocturnal hypoglycaemia which may be asymptomatic. The hypoglycaemic episode is followed by reactive hyperglycaemia due to the action of counter-regulatory hormones such as cortisol, glucagon, epinephrine, and growth hormone acting against the actions of insulin with subsequent increase in hepatic glucose output which manifests as hyerglycaemia in the morning.

The **Dawn phenomenon** differs from the Somogyi effect in that it is not preceded by an episode of hypoglycaemia. It is characterized by an observed increase in blood glucose levels in the morning often between 2 am and 8 am. It is usually seen in all diabetic patients because of the inability to produce compensatory insulin secretion in response to early morning release of counter-regulatory hormones such as cortisol, glucagon, epinephrine, and growth hormone resulting in dysregulated increase in hepatic glucose production seen early morning.

Qb. Why fast-acting insulin analogues are preferred over regular insulin for bolus therapy in the management of diabetes?

While considering bolus insulin therapy the fast-acting insulin analogues are preferred to regular insulin because of the following reasons:

1. Fast-acting insulin analogues dissociate rapidly into monomers, rapidly absorbed with onset of action less than 15 min. Regular insulin forms hexamers which dissociate slowly into monomers thus delaying absorption and the onset of action to ½ to 1 hour.
2. Insulin analogues closely mimics physiological insulin secretion compared to regular insulin which has a relatively longer onset of action and is less likely to match the physiological way the pancreas releases the hormone.
3. The postprandial blood glucose utilization is more efficient with insulin analogues than regular insulins.
4. All rapid-acting insulins provide patients greater flexibility in lifestyle as they can be given at meal times. So, the doses can be adjusted according to the size of meals.
5. There is lesser risk of late postprandial hypoglycaemia because the action of short-acting insulin analogues closely matches with the way the blood glucose levels begin to rise in the body.
6. The action profile of insulin analogues is independent of dose/site of injection/exercise. Therefore, the action is more predictable.

CASE 7: INSULIN RESISTANCE CAUSED BY INSULIN ANTIBODIES

A 45-year-old woman RN has had diabetes for the past 6 years and has been treated with either oral hypoglycaemic agents or insulin. She has been doing well on human NPH insulin for the past several months. However, in the last week, she has developed symptoms of hyperglycaemia. Doubling her insulin dose does not help, and she is admitted to the hospital. Physical examination of the non-obese woman shows no signs of infection, ketoacidosis or Cushing's syndrome. After admission, the insulin dose is increased progressively to 240 units daily but blood glucose concentration never falls below 350 mg/dl.

Qa. What could be the possible explanation for the clinical condition described in case of RN?

The clinical condition described for RN could be due to antibody-mediated insulin resistance because of the presence of hyperglycaemia despite receiving >200 units insulin/day, and a lack of identifiable precipitants for diabetic ketoacidosis or hyperosmolar hyperglyaemic state.

In patients treated with insulin, antibodies can be developed against exogenous insulins, in both type 1 and type 2 diabetes. These insulin receptor antibodies are associated with inhibition of insulin binding to insulin receptors, accelerated receptor degradation, receptor downregulation, and extreme insulin resistance and hyperglycaemia.

CASE 8: DIABETIC KETOACIDOSIS

JK, a 19-year-old man with type 1 diabetes mellitus, presents to the emergency room with drowsiness, fever, cough, diffuse abdominal pain, and vomiting.

His arterial pH is 7.16 with potassium 5.4 mmol/L, bicarbonate 7 mmol/L, phosphate 3.0 mg/dl and glucose 475 mg/dl. Urine analysis showed glucose 800 mg/dl and specific gravity 1030. Ketone bodies in urine was strongly positive.

Your diagnosis: Diabetic ketoacidosis.

Qa. How do you diagnose diabetic ketoacidosis in JK on the basis of clinical presentation and laboratory investigations?

JK has been diagnosed as diabetic ketoacidosis (DKA) characterized by hyperglycaemia, ketosis and metabolic acidosis. In addition, symptoms of fever and cough indicating respiratory tract infection could be the precipitating factor leading to DKA.

Qb. What is the mechanism of diabetic ketoacidosis in type 1 diabetes mellitus patients?

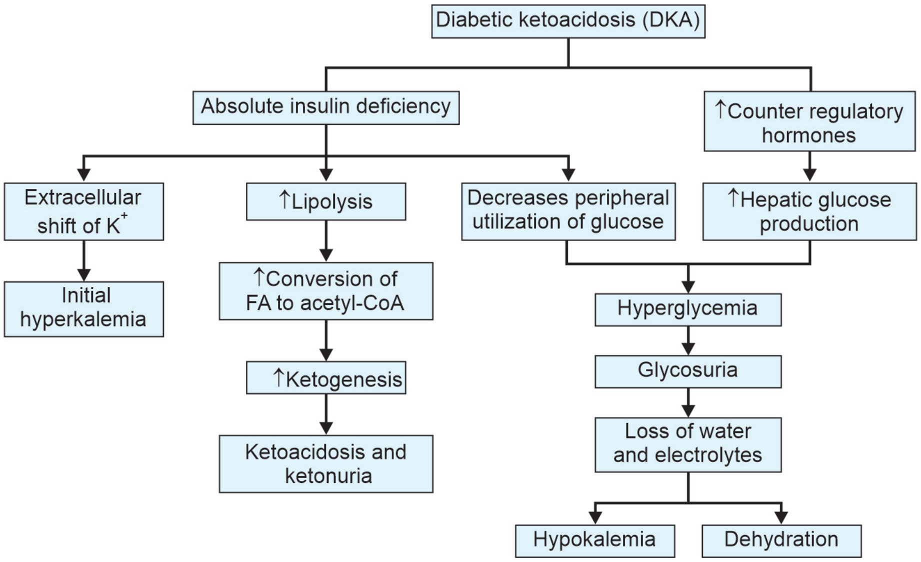

Diabetic ketoacidosis (DKA)
Absolute insulin deficiency
↑Counter regulatory hormones
Extracellular shift of K$^+$
↑Lipolysis
Decreases peripheral utilization of glucose
↑Hepatic glucose production
Initial hyperkalemia
↑Conversion of FA to acetyl-CoA
Hyperglycemia
↑Ketogenesis
Glycosuria
Ketoacidosis and ketonuria
Loss of water and electrolytes
Hypokalemia
Dehydration

Fig. 8.6: Effects of diabetic ketoacidosis

Diabetic ketoacidosis (DKA) mostly occurs in patients with type 1 diabetes. The presumed mechanism of ketoacidosis is the combination of absolute insulin deficiency and increased secretion of glucagon (as well as other counter-regulatory hormones such as cortisol, catecholamines and growth hormone) in response to stress from overwhelming infection, infarction of tissue or other severe illness.

The increased glucagon to insulin ratio causes a mismatch that promotes gluconeogenesis, decreased glucose utilization by the muscle leading to *hyperglycaemia.* Insulin deficiency results in unregulated lipolysis and proteolysis results in uninterrupted formation of ketone bodies known as ketogenesis. The ketone bodies have a low pH and therefore turns the blood acidic (metabolic acidosis).

High serum glucose levels spill into the urine, taking water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. Ketones too participate in osmotic diuresis and lead to further electrolyte losses. This leads to polyuria, dehydration, and compensatory thirst and polydipsia. There is fluctuation in serum K^+ concentration. Initially, there is hyperkalemia due to deficiency of insulin and as the condition becomes severe there is loss of water and electrolytes causing hypokalaemia.

Qc. Discuss the management of diabetic ketoacidosis, a complication of type 1 diabetes mellitus in JK.

The therapeutic goal for the management of diabetic ketoacidosis includes:

- Replacement of fluids and electrolytes
- Suppression of high blood sugars and ketone production with insulin.

Treatment

1. *Correction of dehydration:* Determine hydration status.
    - If severe hypovolemia: Administer 0.9% normal saline (1.0 L/hr)
    - If mild dehydration: Slower rehydration based on calculated water and sodium shortage. The recommended fluid is normal saline.
    - In case of cardiogenic shock: Haemodynamic monitoring and administration of medication that increases the heart pumping action and blood pressure.
2. *Correction of hyperglycaemia:*
    - Insulin regular, 0.1 U/kg of body weight as IV bolus followed by 0.1 U/kg/hr by IV continuous insulin infusion.
    - When serum glucose reaches 200 mg/dl, reduces regular insulin infusion to 0.02–0.05 U/kg/hr IV or gives rapid-acting insulin at 0.1 U/kg SC every 2 hrs. Keep serum glucose between 150 and 200 mg/dl until resolution of DKA.
3. *Maintenance of potassium levels* that fluctuate during the treatment of diabetic ketoacidosis. Insulin drives potassium into the cells decreasing potassium levels in the blood leading to hypokalemia. This increases the risk of dangerous irregularities in the heart rate.
    - If $K^+ < 3.3$ mEq/L: Hold insulin and give K^+ 20–30 mEq/hr until K^+ is greater than 3.3 mEq/L.
    - If K^+ 3.3–5.2 mEq/L: Give 20–30 mEq K^+ in each liter of IV fluid to keep serum K^+ between 4 to 5 mEq/L
    - If $K^+ > 5.2$ mEq/L: Do not give K^+. Check serum K^+ every 2 hours.
4. *Bicarbonate ($NaHCO_3$) treatment* for extreme acidosis (pH <6.9)
5. *Treatment of cerebral edema* if associated with coma by administration of IV mannitol and hypertonic saline.

Qd. Mention the different routes of insulin administration. Which is the common route of insulin administration? Why is insulin not administered by subcutaneous route in DKA?

The primary route of administration for insulin is subcutaneous route. Most of the preparations of insulin are only to be used subcutaneously (SC) with the exception of insulin aspart and insulin lispro which may be used via IV route. Regular insulin, a solution, can be administered by any parenteral route: IV, intramuscularly (IM), or subcutaneously (SC). Afrezza (insulin human) is the only insulin currently available as a powder for inhalation.

Diabetic ketoacidosis (DKA) is characterized by loss of water and electrolytes leading to dehydration. There is reduced blood flow to the skin which slows down the absorption of insulin administered subcutaneously and delays the effects of insulin. Variations in SC absorption can occur, primarily related to changes in blood flow around the injection site.

CASE 9: GLUCOSE TOLERANCE TEST (GTT) IN PREGNANCY FOR DETECTING GESTATIONAL DIABETES MELLITUS (GDM)

A 30-year-old woman VS, is seen in your clinic during her first pregnancy. She is 26 weeks pregnant and has had an uncomplicated pregnancy so far. She has no family history for diabetes mellitus. She has no other significant past medical history. On physical examination she has normal vital signs, including a normal blood pressure. She is not obese.

Qa. A 50 g oral glucose challenge is given to the patient. One hour later a serum glucose level of 150 mg/dl is obtained. What will be the next approach in the management of the patient VS?

American Diabetes Association has recommended the 2-step approach for screening of gestational diabetes. A 50 g, 1-hour glucose challenge test (GCT) is followed by a 100 g, 3-hour OGTT for those with abnormal screening result. Therefore, in case of VS, the test should be repeated with a 100 g glucose challenge and serum glucose levels measured after 3 hours.

Qb. Why testing for gestational diabetes is performed between 24 and 28 weeks of pregnancy?

Gestational diabetes is usually seen in the third trimester. The placenta supplies a growing foetus with nutrients and water, and produces a variety of hormones to maintain the pregnancy. Some of these hormones (estrogen, cortisol, and human placental lactogen) can have a blocking effect on insulin or insulin resistance. This effect usually begins about 20 to 24 weeks into the pregnancy.

As the placenta grows, more of these hormones are produced, and the risk of insulin resistance becomes greater. Normally, the pancreas is able to make additional insulin to overcome insulin resistance, but when the production of insulin is not enough to overcome the effect of the placental hormones, gestational diabetes results. Therefore, screening for gestational diabetes is carried out in between 24 to 28 weeks.

CASE 10: TREATMENT OF GESTATIONAL DIABETES MELLITUS (GDM)

A 30-year-old woman RY, who is 26 weeks pregnant has been diagnosed with gestational diabetes mellitus. Diet and frequent glucose monitoring have failed to decrease her serum fasting glucose to 105 mg/dl.

Qa. What treatment would you recommend for the patient RY?

Insulin therapy remains the standard of care for uncontrolled GDM during pregnancy. Regular insulin, insulin aspart, insulin lispro, NPH, and insulin detemir are included in pregnancy category B. For these insulins, the FDA has received sufficient human data allowing these to be considered as low risk in pregnancy.

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Chapter

9

Antithyroid Drugs and Thyroid Hormones

CASE 1: ANTITHYROID DRUG THERAPY IN HYPERTHYROIDISM

'AB', a 25-year-old female presents to the clinic with complaints of nervousness, heat intolerance and weight loss despite an increased appetite. Neck examination reveals enlarged thyroid gland. There are signs of lid lag and protrusion of eyeball. Family history is suggestive of thyroid disease.

Thyroid function studies reveals the following:

FT4 2.7 ng/dl (normal 0.8–1.8 ng/dl); TSH <0.018 μU/ml (normal 0.5–5 mIU/L); thyroid peroxidase anti-body (TPOAb) 2542 IU/ml (<60).

Your diagnosis: **Graves disease.**

AB was started on methimazole 30 mg/day, orally.

Qa. Classify the drugs available that inhibit the production of thyroid hormones and useful in the management of Graves disease.

The classification of drugs used in the treatment of hyperthyroidism is given below:

A. Thioamide derivatives:
   Propiothiouracil, carbimazole and methimazole

B. Radioactive iodine:
   ^{131}Iodine

C. Iodides:
   Aqueous potassium iodide solution; Lugol's iodine

D. Iodinated contrast media:
   Oral ipodate and ipanoic acid

Qb. Mention the steps in thyroid hormone synthesis. How do thioamides act to control features of thyrotoxicosis?

Thyroid hormone synthesis includes the following steps:

- Iodide (I^-) trapped by the thyroid follicular cells
- Diffusion of iodide to the apex of the cells
- Transport of iodide into the colloid

- Oxidation of inorganic iodide to iodine catalysed by enzyme thyroperoxidase and incorporation of iodine into tyrosine residues within thyroglobulin.
- Two DIT (T_2) molecules join to form T_4, while one MIT (T_1) and one DIT (T_2) join to form T_3.
- After proteolysis, free T_3 and T_4 are then secreted and transported into the plasma.

Thioamides inhibit thyroid hormone synthesis in several steps:

- Inhibition of oxidation of iodide.
- Compete with tyrosine residues in thyroglobin for oxidised iodide so that few tyrosine residues are iodinated.
- Inhibition of coupling of iodotyrosine residues to form T_4 and T_3.

Qc. Why do you think thioamides are preferred over radioactive iodine or surgery considering the case of AB? Give reasons.

Thioamides are preferred over radioactive iodine or surgery in a young female with uncomplicated Graves disease. This is the only therapy where the thyroid gland is intact and the risk of hypothyroidism is less.

Radioactive iodine is the preferred treatment in

- Older patients with clinical features of ophthalmopathy and hyperthyroidism
- Patients with cardiac disease and
- Patients with toxic multinodular goiter

Surgery is the treatment when

- The patient is intolerant to thioamides
- If malignancy is suspected
- In presence of compressive symptoms due to esophageal obstruction, tracheal obstruction or involvement of recurrent laryngeal nerve
- When radioactive iodine therapy is contraindicated

Qd. Why do you think the physician has chosen methimazole over propylthiouracil?

- Compliance is better with methimazole than propylthiouracil because methimazole can be given once daily and fewer tablets are needed as compared to propylthiouracil which is administered three times in a day.
- Patients treated with methimazole become euthyroid sooner.
- Methimazole is safer than propylthiouracil. Propylthiouracil is associated with higher incidence of serious side effects such as hepatotoxicity, hypoprothrombinaemia, agranulocytosis and vasculitis than methimazole.
- The cost of methimazole at lower doses is comparable to propylthiouracil but at higher doses methimazole may be more expensive.

Qe. If AB wishes to conceive, will methimazole adversely affect the foetus? If yes, give reasons. What should be the further line of action?

Methimazole is *not protein-bound* and is *lipid-soluble* and therefore freely crosses placental membrane and breast epithelium and causes foetal harm, especially during the first trimester. Propylthiouracil on the other hand is strongly protein-bound largely to serum albumin and is ionized at physiologic pH. Free (i.e. unbound) drug concentration is low and ionized (non-lipid soluble) drug may not fully cross membranes.

Propylthiouracil is thus, the thioamide of choice in pregnancy. Therapy in AB can be switched from methimazole to propylthiouracil, when planning for pregnancy. However, propylthiouracil should be discontinued 4 weeks before the expected date of delivery, to avoid any possibility of foetal hypothyroidism at the time of maximum brain development.

Qf. Which are the other special circumstances where propylthiouracil is preferred to methimazole?

Besides pregnancy and lactation, propylthiouracil is the thioamide of choice in *neonates*, in patients who are *intolerant to methimazole and refuse radioactive iodine (RAI) therapy or surgery* in uncomplicated thyrotoxicosis.

Qg. While clinical improvement with thioamides takes 3–4 weeks, response to iodides is rapid and effect is seen immediately. Give reasons.

Thioamides *block the synthesis of thyroid hormones*. It has no effect on already synthesized thyroid hormones which are released into the circulation. Therefore, the effect of blockade takes 3 to 4 weeks to be seen. The predominant action of iodides is to *inhibit the release of thyroid hormones* and the onset of action is immediate and therefore rapid response is seen.

Qh. Explain the reasons why iodides should not be used as primary therapy for Graves disease.

Iodides should never be used as primary therapy in Graves disease because with continued use it becomes ineffective. Exogenous iodides used initially, increase intrathyroidal iodide concentration which cause inhibition of intrathyroidal organification of iodides *(known as Wolff Chaikoff effect)* and this is not overcome by TSH stimulation. The resultant effect is decrease in serum T_3 concentration, which helps in reducing symptoms of thyrotoxicosis.

On prolonged use, the *gland can escape block* due to decreased iodide transport and leaking iodide decreasing intrathyroidal iodide concentrations. This allows TSH to stimulate the synthesis and release of thyroid hormone. Therefore, when used for a prolonged period it fails to control serum T3 levels and symptoms of thyrotoxicosis.

Qi. What are the other important uses of iodide in patients with thyroid disease?

Other important uses of iodide are the following:
- For preparation of patients for surgery
- Treatment of thyrotoxic storm
- After radioiodine treatment

Case Continued

The lady 'AB' was admitted to the hospital one year later with complaints of high fever, nausea, vomiting, abdominal pain, diarrhoea, shortness of breath and palpitation. The patient was agitated, restless and confused. On examination, there was tachycardia (124 beats/min), tachypnea and blood pressure of 170/100 mmHg.

There was diffusely enlarged thyroid gland with bruit and bilateral exophthalmos. Further questioning reveals that she has been irregular in taking her medication.

Urine test suggests urinary tract infection.

The patient had been non-compliant with treatment for Graves disease for past 4 months. The clinical presentation and physical findings suggest a diagnosis of 'thyrotoxic crisis'. Urinary tract infection may be the precipitating factor for thyrotoxic crisis.

Qa. What are the treatment strategies in the management of thyrotoxic crisis?

I. Reduction of thyroid hormone production and secretion

- Inhibition of T_4 and T_3 synthesis
  - Propylthiouracil and methimazole
- Inhibition of T_4 and T_3 secretion
  - Inorganic iodide (potassium iodide, Lugol's solution)
  - Thyroidectomy on emergent basis

II. Therapy directed against systemic disturbances

- Treatment of fever
  - Acetaminophen
  - External cooling
- Correction of volume depletion and poor nutrition
  - Intravenous fluid and electrolytes
  - Glucose
  - Vitamins
- Supportive therapy
  - Oxygen
  - Vasopressor drugs
- Treatment for congestive heart failure (diuretics and digoxin)

III. Amelioration of the peripheral actions of thyroid hormone

- Inhibition of extrathyroidal conversion of T_4 to T_3
  - Propylthiouracil
  - Glucocorticoids
  - Propranolol
- Removal of T_3 and T_4 from serum
  - Cholestyramine, plasmapheresis, hemodialysis and hemoperfusion

IV. Treatment of any precipitating or underlying illness

Qb. What is the rationale for the use of propylthiouracil, iodides, glucocorticoids and propranolol in the management of thyroid storm?

Propylthiouracil: Propylthiouracil has an advantage over methimazole because of its dual action of causing inhibition of T_4 and T_3 synthesis in the thyroid and extrathyroidal conversion of T_4 to T_3 thereby reducing serum T_3 concentration and also the clinical manifestations of thyrotoxicosis more rapidly than methimazole.

Iodides: Iodides block the release of already synthesized T_3 and T_4 in the thyroid and thereby help in controlling the symptoms of hyperthyroidism.

Glucocorticoids are administered to avoid the risk of relative adrenal insufficiency associated with thyrotoxic crisis, decrease the peripheral conversion of T_4 to T_3 in thyrotoxicosis and also directly inhibit the secretion of thyroid hormone.

Propranolol shows beta-adrenergic blockade and attenuates the effects of catecholamines and provides relief from symptoms of thyrotoxicosis notably anxiety, palpitation, tremor and heat intolerance and reducing heart rate and cardiac output, thus exhibiting beneficial action on the cardiovascular system.

CASE 2: RADIOACTIVE IODINE TREATMENT IN HYPERTHYROIDISM

A 45-years-old female patient 'CD' married and completed family, presents with features of hyperthyroidism, diagnosed as Graves disease was started on methimazole. Two weeks later she reported to the clinic with maculopapular rash pruritic in nature, high fever, joint pain and tenderness. Methimazole was the suspect drug and was stopped. Amongst the available options, the patient preferred radioactive iodine treatment.

Qa. How does RAI therapy act in controlling thyrotoxicosis in Graves disease? What do you think are the reasons for the patient to have opted for RAI therapy?

^{131}I is the isotope of choice used in the treatment of thyrotoxicosis in Graves disease. ^{131}I is administered orally as a single dose in a capsule or in water, is rapidly and completely absorbed and is quickly concentrated, oxidized and organified by thyroid follicular cells. Radioactive iodine emits both gamma radiation and beta-particles. It is the ionizing effect of beta-particles which have a path length of 1 to 2 mm that destroy thyroid follicular cells.

RAI therapy is effective, safe, easy to administer and inexpensive but it is contraindicated in pregnancy. Clinical history reveals that the patient 'CD' has completed family and does not wish to conceive. Also the drug history suggests that the patient is intolerant to methimazole. Thus, RAI therapy is an ideal choice for this patient.

CASE 3: SURGERY AS TREATMENT FOR HYPERTHYROIDISM

A 27-year-old female patient 'XY', presented to the clinic for the evaluation of neck mass which she observed was gradually enlarging in last 6 months. She experiences neck pain, shortness of breath and difficulty in swallowing for last one week. On questioning further she revealed that she first noticed the swelling in the neck 2 years back. It was painless and recently it has been causing trouble. Family history indicates her mother had died of thyroid cancer. She denies any unusual exposure to ionizing radiation. Thyroid function studies reveal normal TSH and serum T_4 levels. Fine needle aspiration cytology report showed malignancy.

Qa. What is the appropriate treatment for the patient 'XY'?

The patient has been confirmed with malignancy. Compressive symptoms which occur from thyroid enlargement and impingement on adjacent structures, most notably the trachea, esophagus and recurrent laryngeal nerve causing symptoms of dyspnea, trouble in swallowing and a change in voice are indications for surgery.

Therefore, surgery is the definite treatment for this patient.

Qb. Why should the patient be made euthyroid prior to surgery? What are the drugs used to maintain euthyroidism?

To avoid precipitation of thyroid storm and morbidity in patients operated for thyroid surgery, the patient should be made euthyroid. The drugs used to maintain euthyroidism are *thioamides, iodides and propranolol.* Potassium iodide (KI) is often prescribed prior to thyroidectomy. It is generally thought to decrease vascularity and make surgery easier by reducing the intraoperative blood loss.

CASE 4: THYROID HORMONE REPLACEMENT THERAPY FOR HYPOTHYROIDISM

A 35-year-old female patient 'PR' presents to the clinic with complaints of lethargy, fatique, and mental sluggishness. Her menses have become light and irregular. Her facial appearance is puffy. She has recently gained weight of 10 kg. On physical examination, the thyroid

gland appears enlarged and firm. There is delayed relaxation of deep tendon reflexes. Laboratory findings show low FT4, an elevated TSH value and positive thyroid peroxidase anti-bodies.

The case was diagnosed as 'Hashimoto thyroiditis'.

Qa. How do you think the physician has arrived at this diagnosis?

Presence of a firm goitre, detection of thyroid peroxidase anti-bodies and clinical symptoms of hypothyroidism such as weight gain, mental fatique, lethargy, irregular menses and the laboratory findings strongly suggest Hashimoto thyroiditis.

Qb. What are the therapeutic goals in the patient 'PR'?

The therapeutic goals in this patient are as follows:

- Clinical improvement in the signs and symptoms of hypothyroidism
- Normalization of laboratory parameters

Qc. What should be the treatment of choice for the patient 'PR'?

Levothyroxine or L-thyronine is the thyroid hormone replacement of choice. It has a long half-life of 7 days which permits once a day dosing. Absorption is optimal on an empty stomach. Current guidelines recommend taking levothyroxine within 60 minutes before breakfast or 3 to 4 hours after the evening meal for consistent absorption.

CASE 5: MANAGEMENT OF MYXEDEMA COMA

A 64-year-old male 'MN' presented to the emergency department with an altered mental status. According to the patient's caregivers, the patient had become less responsive and increasingly confused over the last 24 hours. The patient was not communicative and was in mild distress with breathing difficulty.

Physical examination: **Blood pressure 109/76 mmHg, heart rate 49 bpm, rectal temperature 32.9°C (normal temperature is 34.4 to 37.8°C), skin—cool, dry, and non-edematous.**

Cardiovascular examination: **Bradycardia with a regular rhythm, and without murmurs, distal pulse—faint and bilaterally appreciable, the ECG revealed a bradycardic junctional rhythm with a rate of 49 bpm along with a prolonged QT interval.**

Laboratory examination is significant for elevated TSH levels—83.37 µU/ml (normal levels—0.5 to 5.0 µU/ml), low free T_3 and free T_4 levels.

She was diagnosed with myxedema coma after not taking her thyroid medications for six weeks. The patient was endotracheally intubated for protection of his airways and was admitted to the intensive care unit.

Qa. Mention the clinical features that are consistent with the diagnosis of myxedema coma.

The cardinal features of myxedema coma are the following:

1. Hypothermia
2. Altered mental status and
3. Cardiovascular depression

In case of MN, the signs and symptoms suggestive of myxoedema coma are confusion or unresponsiveness, low body temperature, respiratory difficulty, low blood pressure and heart rate. The thyroid tests reveal elevated TSH values and reduced T_3 and T_4 levels.

Qb. Explain the reason for the above described clinical presentation.

Myxedema coma in patient MN could have resulted from stopping the medications for treatment of hypothyroidism and is precipitated by infection.

Note: Myxedema coma can result from any of the causes of hypothyroidism, most commonly chronic autoimmune thyroiditis. It can also occur in patients who had thyroidectomy or underwent radioactive iodine therapy for hyperthyroidism.

Qc. Outline the management of the patient MN, a case of myxedema coma.

The steps in the management of myxedema coma include the elements described below:

1. Airway Management

Maintenance of adequate airway is crucial since most patients have depressed mental status along with respiratory failure. Mechanical ventilation is commonly required during the first 36 to 48 hours.

2. Thyroid Hormone Replacement

The American Thyroid Association recommends combination therapy with T_4 and T_3. Because the rate of conversion of T_4 to the active hormone T_3 can be reduced in these patients, the addition of T_3 along with T_4 has been recommended. Intravenous thyroid hormone therapy is advised because of reduced gastrointestinal absorptions.

Intravenous levothyroxine treatment in severely hypothyroid patients usually leads to improvement in cardiovascular, renal, pulmonary and metabolic parameters within a week. Serum T_4 and T_3 concentration may improve or normalize with a similar time frame, with more gradual improvement in serum TSH.

Thus, the therapeutic end-points in myxedema coma should be improved mental status, improved cardiac function and improved pulmonary function.

3. Glucocorticoid Therapy

Intravenous glucocorticoids, hydrocortisone or dexamethasone is administered. This is necessary because patients with primary hypothyroidism may have concomitant primary adrenal insufficiency, while patients with secondary hypothyroidism may have associated hypopituitarism and secondary adrenal insufficiency. The other rationale for treatment with corticosteroids is the potential risk of precipitating acute adrenal insufficiency caused by the accelerated metabolism of cortisol that follows T_4 therapy.

4. Supportive Measures

Hypothermia is treated with passive rewarming and associated infection is treated with empirical anti-biotics. Severe hyponatremia is corrected with saline and free water restriction. Hypotension is usually corrected with thyroid hormone therapy.

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Chapter

10

Drugs for Osteoporosis

CASE 1: MANAGEMENT OF A CASE OF POSTMENOPAUSAL WOMEN IN EARLY MENOPAUSAL PHASE WITH ESTABLISHED OSTEOPENIA AND RISK FACTORS FOR FRACTURE

TN, a 50-year-old female, thin built, low body mass index, presents with hot flashes causing night time awakening and subsequent fatigue, vaginal dryness despite use of adequate lubricants causing dyspareunia and decreased libido. There is history of recurrent urinary tract infections and is treated with antibiotics.

She is hypertensive, diabetic, with history of hyperthyroidism and is on treatment with drugs. Her mother had suffered from hip fracture.

Investigations reveal vitamin D deficiency, bone mineral testing shows T score of –2 suggesting osteopenia.

Qa. Describe 'bone remodelling' and its role in health and disease.

There are two phases of bone remodelling: Resorption and ossification. Bone remodelling is mediated by a balance of osteoblast and osteoclast cell activity, which together, maintain bone mass and mineral homeostasis.

In the *resorption phase,* the formation and activity of osteoclasts is controlled by cells of the osteoblast lineage that recruit osteoclast precursors to the remodelling site. There is expression of RANK ligand on the osteoblasts which interact with RANK receptor on osteoclasts. This results in bone resorption.

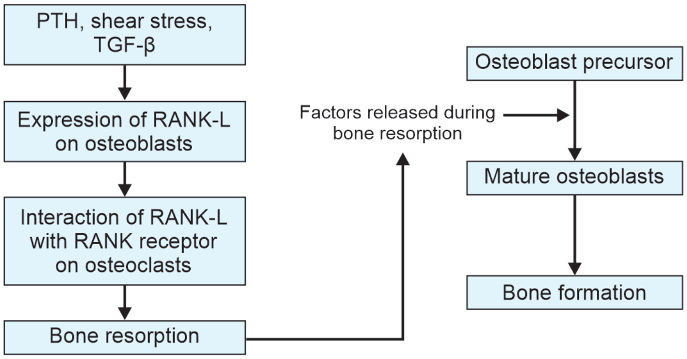

PTH, shear stress, TGF-β
Expression of RANK-L on osteoblasts
Interaction of RANK-L with RANK receptor on osteoclasts
Bone resorption
Factors released during bone resorption
Osteoblast precursor
Mature osteoblasts
Bone formation

Fig. 10.1: Bone remodelling: Resorption and ossification

In the *reversal phase*, the osteoclasts undergo apoptosis whilst osteoblasts are recruited and begin to differentiate, therefore the reversal phase is a transition from osteoclast to osteoblast activity.

In the *termination phase*, the osteocytes may secrete inhibitory factors that slow down the rate of bone formation as the resorbed cavity is nearly filled.

Calcitonin, PTH, vitamin D_3 and estrogen are the major hormonal regulators of osteoclastic bone resorption. Some of the clinical conditions where bone remodelling is perturbed and there is increased osteoclast activity are hyperparathyroidism and osteoporosis.

Qb. What are the drugs available for the prevention and treatment of osteoporosis?

Drugs used for the prevention and treatment of osteoporosis		
Antiresorptive drugs	**Hormone replacement therapy (HRT)**	Estrogen therapy, estrogen progestogen therapy
	Selective estrogen receptor modulators (SERM)	Raloxifene, tamoxifene
	Bisphosphonates	Alendronate, risedronate, etidronate, ibandronate
	Calcitonin	
Bone forming drugs	**Parathyroid hormone**	Teriparatide
Drugs with complex mechanism of action		Strontium ranelate, vitamin D, denosumab

Case Continued

Mrs TN is a postmenopausal woman with risk factors for fracture such as hyperthyroidism, vitamin D deficiency and positive family history of fracture with severe menopausal symptoms. Also, the BMD is –2, which is suggestive of osteopenia. She was prescribed estrogen–progesterone therapy by her physician.

Qa. What are the benefits and risks associated with hormone replacement therapy (HRT) initiated in early menopausal years?

Starting hormone replacement therapy **(**HRT) in the early menopausal years is associated with relief of vasomotor symptoms, prevention of urogenital atrophy causing dyspareunia, and reduction of the rapid bone loss that is prevalent in untreated women during the first 5 to 7 years following menopause. Use of HRT during the early menopausal years may also be associated with a reduction in the risk of coronary heart disease.

The risks associated with HRT include venous thromboembolism (VTE), greater risk of increased breast density and increased risk of gallbladder disease. The increased risk of breast cancer in women on short term HRT remains debatable. However, the risk of breast cancer, endometrial cancer, VTE, stroke increases with continued use of HRT for 5 years or more.

Qb. Was the hormone replacement therapy (HRT) prescribed in case of TN for the relief of menopausal symptoms and prevention of osteoporosis justified? Explain.

In general, the benefits of hormone replacement therapy (HRT) outweigh the risks in symptomatic menopausal women under the age of 60. HRT started early in postmenopausal women significantly reduced death rate, heart attacks and heart failure. Considering the benefits of HRT, estrogen therapy and estrogen–progesterone therapy should be used at the lowest effective doses and for the shortest duration indicated.

Case Continued

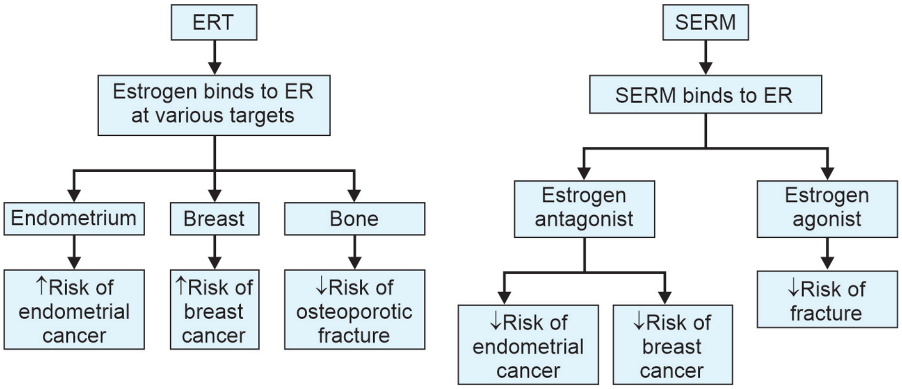
3 months later after the relief of menopausal symptoms TN's medication was switched from hormone replacement therapy (HRT) to raloxifene, a selective estrogen receptor modulator (SERM).

Qa. What are selective estrogen receptor modulators (SERMs)? Which SERM is approved the prevention and treatment of osteoporosis in postmenopausal women?

Selective estrogen receptor modulators (SERMs) constitute a group of chemical compounds that are distinct from estrogen, lacking the basic steroid structure of sex hormones but they bind and interact with estrogen receptors and possess estrogen agonist or antagonist properties at different target tissues.

Raloxifene is approved for the prevention and treatment of osteoporosis in postmenopausal women.

Qb. What are the benefits of raloxifene over hormone replacement therapy (HRT), when used in the management of postmenopausal osteoporosis as in case of TN?


ERT
Estrogen binds to ER at various targets
Endometrium
Breast
Bone
↑Risk of endometrial cancer
↑Risk of breast cancer
↓Risk of osteoporotic fracture
SERM
SERM binds to ER
Estrogen antagonist
Estrogen agonist
↓Risk of endometrial cancer
↓Risk of breast cancer
↓Risk of fracture

ERT: Estrogen replacement therapy; SERM: Selective estrogen receptor modulator
ER: Estrogen receptor

Fig. 10.2: Comparative effects of estrogen replacement therapy and selective estrogen receptor modulator in postmenopausal osteoporosis

The goal of SERM is to retain the beneficial effects of ERT while eliminating the undesirable effects of estrogen therapy. Raloxifene reduces bone resorption and increases bone density, but is less potent than either estrogen or bisphosphonates in this regard. It decreases the incidence of vertebral fractures, but it has not been shown to have any effect on non-vertebral fractures. The anti-estrogen actions of raloxifene block proliferative effects of the estrogen on breast and endometrial cells, thus lowering the risk of breast cancer and endometrial cancer.

Hormone replacement therapy causes relief of menopausal symptoms and prevents bone loss but increases the risk of breast cancer and endometrial cancer.

Raloxifene may be used as an alternative to hormone replacement therapy in postmenopausal women for the prevention and treatment of osteoporosis without adversely affecting the breast and the endometrium.

Qc. Why is raloxifene and not tamoxifene selected for the prevention and treatment of osteoporosis in a postmenopausal woman?

Tamoxifene is a selective estrogen receptor modulator, similar to raloxifene in its actions on bone and breast and helps to preserve the bone mass and reduce the risk of breast cancer but can *lead to increased proliferation in the endometrial tissue* because of estrogen agonist action on the uterus increasing the risk of endometrial cancer. In contrast, raloxifene does not adversely affect the uterus due to lack of stimulant action on the uterus. Therefore, raloxifene is preferred to tamoxifene for the prevention and treatment of osteoporosis in a postmenopausal woman.

Qd. What are the risks associated with raloxifene use in postmenopausal osteoporosis treatment?

The *risk of venous thromboembolism and stroke* is of particular concern for women on treatment with raloxifene, who have an elevated risk of this outcome, including overweight women and those of advanced age. Also there is an *increased incidence of vasomotor symptoms*. Raloxifene can cause leg cramps and hot flashes often limiting its use in the immediate postmenopausal years.

CASE 2: A CASE OF SEVERE OSTEOPOROSIS WITH FRAGILE FRACTURE AND CO-EXISTING MEDICAL CONDITIONS SUCH AS RHEUMATOID ARTHRITIS, DIABETES AND HYPERTENSION

KL, a 70-years-old female, presents with a complaint of back pain for last one week. There is no history of fall and no significant joint pain or swelling.

She was diagnosed with rheumatoid arthritis 10 years ago and is on treatment with methotrexate and hydroxychloroquine. She has taken glucocorticoids on several occasions for a brief period for relief of joint pain and swelling. The patient is diabetic for last 15 years and hypertensive for last 5 years.

BMD of spine is –3 and vertebral imaging shows fracture.

KL was prescribed bisphosphonates for the management of the clinical condition.

Qa. How do bisphosphonates play a role in the treatment of osteoporosis?

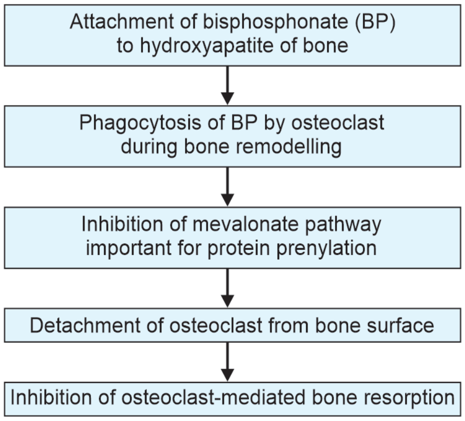

Attachment of bisphosphonate (BP) to hydroxyapatite of bone
Phagocytosis of BP by osteoclast during bone remodelling
Inhibition of mevalonate pathway important for protein prenylation
Detachment of osteoclast from bone surface
Inhibition of osteoclast-mediated bone resorption

Fig. 10.3: Mechanism of action of bisphosphonates (BP)

Nitrogen-containing bisphosphonates include alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid, are potent antiresorptive agents and widely used. They have strong affinity for hydroxyapatite of bone and concentrated in mineralised matrix. During remodelling, osteoclasts dissolve the matrix releasing the bisphosphonates which are phagocytosed by the osteoclasts. Inside the osteoclast, they work by inhibiting farnesylation and geranylation which are very important in anchoring of proteins to the cell membrane, known as protein prenylation. Protein prenylation enables the osteoclasts to localize to specific target membranes. Inhibition of protein prenylation causes the osteoclast to detach from the bone surface, with inhibition of osteoclast activity and apoptosis of osteoclasts.

Qb. What are the common side effects associated with bisphosphonates, used in the treatment of osteoporosis?

Common adverse effects associated with the use of oral bisphosphonates include gastrointestinal symptoms such as flatulence, constipation or diarrhea, abdominal pain and acid regurgitation. IV bisphosphonates are known to cause acute phase reaction with transient pyrexia myalgias, arthralgias, headaches, and influenza-like symptoms.

Qc. What are the safety concerns related to long term use of bisphosphonates?

Long term use and higher doses of bisphosphonates may be associated with osteonecrosis of the jaw and atypical fractures of the femoral shaft.

Qd. KL was advised to take bisphosphonates after an overnight fast early in the morning with substantial amount of water followed by a postdose fast of 30 minutes and remain upright during the postdose fasting period. Explain why?

Oral bisphosphonates are *poorly absorbed in the gastrointestinal tract* and have very less bioavailability. So, taking the drug early in the morning in empty stomach with substantial amount of water enhances absorption of the drug with greater bioavailability. *Esophageal adverse effects, such as esophagitis, esophageal ulcers, and erosions*, have occurred in patients who do not take bisphosphonates with sufficient amount of water and do not remain upright after taking bisphosphonates. In order to minimize contact of the drug with the esophagus, KL was advised to remain upright during the postdose fasting period.

*(**Note:** Oral bisphosphonates are contraindicated in abnormalities of the esophagus such as achalasia, esophageal stricture, esophageal varices, Barrett's esophagus, inability to stand or sit upright for at least 30 minutes.)*

Qe. Mention the clinical conditions other than osteoporosis where bisphosphonates are used.

Bisphosphonates are also approved for the treatment of hypercalcemia of malignancy, Paget disease of the bone, and in malignancies with metastasis to the bone.

Case Continued

2 years later, the medication for KL was switched from bisphosphonates to teriparatide, a human recombinant parathyroid hormone, for the treatment of osteoporosis.

Qa. Explain why teriparatide, human recombinant parathyroid hormone is used in the treatment of osteoporosis when it is well known that high PTH levels in hyperparathyroidism contribute to bone loss.

Intermittent administration of teriparatide, human recombinant parathyroid hormone favours bone anabolism while high continuous exposure to parathyroid hormone favours bone catabolism. Teriparatide when given subcutaneously in intermittent low doses, stimulate osteoblast-mediated bone formation resulting in an increase in trabecular thickness and number. It also has benefits on fracture healing. Callus formation is accelerated by stimulation of proliferation and differentiation of osteoprogenitor cells and increases in production of bone matrix. In contrast continuous exposure to high levels of

PTH increases the number of bone resorbing osteoclasts leading to increased bone resorption.

Therefore, teriparatide when administered in a dose of 20 µg injected daily subcutaneously increases BMD and decreases the risk of vertebral and non-vertebral fractures in postmenopausal women and improves fracture healing.

Evidence suggests that it has shown higher efficacy in glucocorticoid-induced osteoporosis than bisphosphonates. Moreover, teriparatide is a suitable option for the treatment of postmenopausal women with severe vertebral osteoporosis.

CASE 3: A CASE OF SECONDARY OSTEOPOROSIS

A 60-year-old female RM, with complaints of pain and stiffness in joints and weakness predominantly affecting the proximal muscles of the limbs, fatique. She was diagnosed with diabetes 14 years ago and hypertension 20 years ago. Recently, she required drug intensification for blood pressure control.

Laboratory investigations reveal elevated serum BUN, creatinine and GFR <30 ml/min indicative of chronic kidney disease.

Other significant findings include hypocalcemia, hyperphosphatemia, increased PTH levels and reduced calcitriol. Also, there are anaemia and raised alkaline phosphatase levels.

Qa. What is the pathophysiologic basis for the laboratory findings including hyperphosphatemia, reduced calcitriol, hypocalcemia and increased PTH levels in chronic kidney disease?

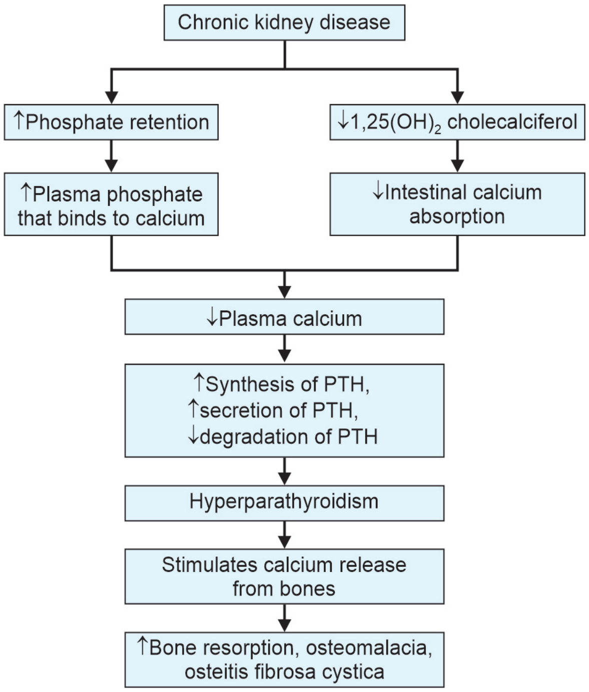

Chronic kidney disease
↑Phosphate retention
↓1,25$(OH)_2$ cholecalciferol
↑Plasma phosphate that binds to calcium
↓Intestinal calcium absorption
↓Plasma calcium
↑Synthesis of PTH,
↑secretion of PTH,
↓degradation of PTH
Hyperparathyroidism
Stimulates calcium release from bones
↑Bone resorption, osteomalacia, osteitis fibrosa cystica

Fig. 10.4: Chronic kidney disease-induced osteoporosis

When the renal function declines in chronic kidney disease, there is *hyperphosphatemia* and the ability to produce renal hydroxylated 1,25-vitamin D diminishes resulting in decreased *1,25-dihydroxy vitamin D levels.*

High levels of phosphate in the plasma form complex with calcium, and decreased activity of calcitriol reduces the intestinal absorption of calcium causing *hypocalcemia.*

Sustained hypocalcemia stimulates synthesis and secretion of PTH and induces parathyroid gland hypertrophy and hyperplasia leading to secondary hyperparathyroidism. Hyperparathyroidism and accelerated bone metabolic turnover associated with renal dysfunction begin to develop CKD patients with an estimated glomerular filtration rate of <60 ml/min. Hyperparathyroidism gives rise to bone resorption with an increase in the risk of hip fracture and forearm fracture.

Qb. What is the role of vitamin D analogues in the management of bone mineral disease associated with chronic kidney disease?

Incomplete hydroxylation to active form of vitamin D which is $1,25(OH)_2D$ in chronic kidney disease results in decreased intestinal absorption of calcium and fall in plasma calcium levels leading to secondary hyperparathyroidism. *Vitamin D and analogues are approved for the treatment of secondary hyperparathyroidism.*

Active vitamin D congeners bypass the need for 1α-hydroxylation in the kidney, increasing the dietary absorption of calcium in the intestine that is followed by a subsequent rise in plasma calcium levels and suppression of the secretion of parathyroid hormone by parathyroid gland. In addition, these agents bind to and activate vitamin D receptors on the chief cells and thereby *suppress PTH gene transcription and secretion of PTH*.

Qc. How is paricalcitol, a synthetic analog of vitamin D superior to calcitriol [$1,25(OH)_2D_3$] in the treatment of secondary hyperparathyroidism?

PTH levels are elevated in response to low plasma calcium concentration in chronic kidney disease. Calcitriol [$1,25(OH)_2D_3$] suppresses PTH secretion by raising the calcium concentration but simultaneously *leading to unwanted hyperphosphatemia*. Therefore, calcitriol should not be administered to patients with chronic kidney disease until hyperphosphatemia has been controlled with diet and pharmacologic agents. Paricalcitol, a synthetic analog of vitamin D *lowers plasma PTH levels with no significant effect on plasma calcium or phosphate levels.* Therefore, paricalcitol is preferred to calcitriol in the treatment of secondary hyperparathyroidism.

Qd. How does cinacalcet act in the treatment of secondary hyperparathyroidism?

Cinacalcet is FDA-approved calcimimetic for the treatment of secondary hyperparathyroidism. It directly lowers parathyroid hormone levels by *increasing the sensitivity of the calcium sensing receptors located on the parathyroid gland to activation by extracellular calcium*, resulting in the inhibition of PTH secretion and is useful in the management of hyperparathyroidism.

Qe. What are the various phosphate binding agents used to control hyperphosphatemia in chronic kidney disease with associated bone mineral disorder?

Phosphate binders decrease the intestinal absorption of phosphate and lower serum phosphorus levels and control hyperparathyroidism-induced bone loss. Various phosphate binders include aluminium hydroxide, oral preparations of calcium carbonate and calcium acetate and sevelamer.

Aluminium hydroxide causes long-term risk of aluminium toxicity, anaemia, osteomalacia and neurotoxicity. Therefore, use is restricted to refractory hyperphosphatemia.

Oral preparations of calcium carbonate and calcium acetate lower plasma phosphate but can also cause iatrogenic hypercalcemia and may increase the risk of vascular calcifications.

Sevelamer is a cationic ion exchange resin that binds intestinal phosphate. It also binds bile acids leading to interruption of the enterohepatic circulation and to decreased cholesterol absorption.

Qf. Is it safe to prescribe bisphosphonates or teriparatide for the management of osteoporosis in patients with chronic kidney disease? Explain with reasons.

All bisphosphonates oral and IV, are excreted via the kidney. So, in the advanced stage of chronic kidney disease, the bisphosphonates accumulate in the bone and exert excessive antiresorptive action which causes oversuppression of bone turnover or a dynamic bone condition characterized by low bone turnover. This increases the risk of fracture in chronic kidney disease. Therefore, bisphosphonates should be avoided or used with caution in patients with GFR <30 ml/min. Careful administration is also necessary for parenteral teriparatide due to the potential for serum calcium elevation.

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Chapter

11

Corticosteroids

CASE 1: CASE OF PRIMARY ADRENAL INSUFFICIENCY (PAI)

A 42-year-old female AB, presented to the hospital with history of dizziness and fainting attack. She further reported that in recent months, she has been experiencing nausea, vomiting, loss of appetite, weakness, fatigue, increased salt cravings and abdominal pain. She reported a weight loss of 10 kgs in 4 months.

On examination, she was noted to have mild skin pigmentation. Blood pressure was low. Laboratory investigations suggest electrolyte imbalances (hyponatremia and hyperkalemia). Medical history suggests, AB has diabetes controlled with medications.

Morning cortisol level was low, with very high adrenocorticotropic hormone (ACTH). ACTH stimulation test (cosyntropin test) was performed which suggested that the adrenal gland is not producing enough cortisol. Tuberculin skin test and QuantiFERON test were positive. CT scan of abdomen and pelvis showed diffuse enlarged adrenal glands with areas of lucency reflecting caseous necrosis. The adrenal biopsy suggests tuberculosis.

Your diagnosis: **Primary adrenal insufficiency secondary to tuberculosis.**

Qa. What are the signs and symptoms in AB that are consistent with the diagnosis of adrenal insufficiency secondary to tuberculosis?

AB has classic manifestations of adrenal insufficiency: Nausea, vomiting, loss of appetite, weakness, fatigue, increased salt cravings and abdominal pain. The blood pressure is low and laboratory abnormalities include hyponatremia and hyperkalemia. In addition, the response to cosyntropin test determines adrenal insufficiency. Positive tuberculin skin test, QuantiFERON test and adrenal biopsy confirms adrenal tuberculosis as an association to adrenal insufficiency.

Qb. Why is it important to distinguish primary adrenal insufficiency from secondary adrenal insufficiency in the treatment of AB?

Primary adrenal insufficiency (PAI) is caused by *impairment of function of the adrenal gland itself* most commonly caused by autoimmune-mediated adrenalitis, infection or due to inborn disruption of adrenal cortisol production in congenital adrenal hyperplasia.

Secondary adrenal insufficiency (SAI) is caused by *disruption of the hypothalamic-pituitary-adrenal axis with insufficient stimulation of the adrenal gland due to inadequate secretion and synthesis of ACTH.* This is often caused by pituitary diseases/tumours or their subsequent treatment including surgery and radiotherapy.

The differentiation between PAI and SAI is crucial as it allows clinicians to target therapy to associated deficiencies. In PAI, all steroid hormones synthesised by the adrenal gland are deficient (aldosterone, cortisol and sex steroids), whereas in SAI only hormones that are predominantly controlled by ACTH (cortisol and sex steroids) are deficient, aldosterone replacement is not required as it is controlled by the renin–angiotensin–aldosterone system.

Case Continued

AB was started on anti-tubercular therapy and adrenal replacement therapy. As glucocorticoid replacement therapy, hydrocortisone acetate at a lower dose of 15–20 mg/day divided into two doses (10–15 mg on awakening and 5 mg in late afternoon) was administered. Fludrocortisone acetate was given in a dose of 0.05–0.2 mg/day.

Qa. Why two-thirds of the glucocorticoid dose was given in the morning and one-third in the afternoon?

The normal diurnal rhythm of cortisol secretion is characterized by high levels upon waking, a steep morning rise, and subsequent steeper decline throughout the day. In an effort to mimic the circadian cortisol rhythm in humans, hydrocortisone acetate, a glucocorticoid, is given at a lower dose of 15–20 mg/day divided into two doses (10–15 mg on awakening and 5 mg in late afternoon). Two-thirds of the glucocorticoid dose was given in the morning and one-third in the afternoon.

Qb. Do you think it is necessary to prescribe fludrocortisone acetate together with hydrocortisone in case of AB?

AB is suffering from primary adrenal insufficiency due to tuberculosis. This results in deficiency of both aldosterone and cortisol. Therefore, it is necessary to prescribe fludrocortisone acetate together with hydrocortisone.

Over a period of 2 years, AB experienced weight gain, moon face swelling of eyes, a rise in blood pressure and uncontrolled blood glucose levels. When the side effects became intolerable to AB, she discontinued her medicines without seeking medical advice in an attempt to avoid side effects.

Qc. What are the short-term and long-term adverse effects of oral corticosteroid use?

Short-term oral corticosteroid use	*Long-term oral corticosteroid use*
Glucose metabolism abnormalities	Adrenal axis suppression
Increased appetite	Growth suppression
Fluid retention	Dermal thinning
Weight gain	Hypertension
Hypertension	Diabetes
Peptic ulcer	Cushing’s syndrome
Mood alteration	Cataracts
	Muscle weakness
	Impaired immune function

Qd. What is the likely reason for weight gain and typical appearance of ‘moon face’, ‘buffalo hump’ and truncal obesity?

Long-term administration of corticosteroids can cause a rise in blood sugar levels which induce secretion of insulin resulting in elevated levels of insulin. The lipogenic action of insulin leads to fat deposition preferentially towards the central locations because the adipocytes in the trunk region show increased sensitivity to insulin. At the peripheral locations there is decreased sensitivity of adipocytes to insulin and increased lipolytic effects of growth hormone, adrenaline and thyroxine. The glucocorticoids, thus cause centripetal obesity with fat deposits at the back of the neck and shoulders (buffalo hump), abdomen and face (moon face) and peripheral thinning of limbs.

Qe. Considering that AB is a patient of diabetes, what are the underlying mechanisms that could lead to alteration of blood glucose levels associated with hydrocortisone use?

The use of hydrocortisone in a patient with pre-existing diabetes is likely to worsen the glucose levels of the blood and this may be termed as 'steroid-induced hyperglycemia'. This is caused by various mechanisms which include:

- Reduction in peripheral glucose uptake at the level of muscle and adipose tissue.
- Increased gluconeogenesis resulting in endogenous glucose production by activating numerous genes involved in the hepatic metabolism of carbohydrates.
- Inhibition in the production and secretion of insulin from pancreatic β-cells.

Qf. What advice would you give to the patient AB who is under long-term treatment with hydrocortisone, with regard to blood glucose control?

The patient should be advised to monitor blood sugar levels and if needed will require additional and more active glycaemic management in presence of hydrocortisone. The insulin dose may be increased or oral hypoglycemic medications should be added to maintain normal blood glucose levels.

Qg. How does glucocorticoid induce osteoporosis and increase the risk of fractures, when used for long-term in AB, who is at her perimenopausal age?

High dose and long-term use of glucocorticoids lead to glucocorticoid-induced osteoporosis and the risk of fractures increase with age. The mechanisms which contribute to glucocorticoid-induced osteoporosis are the following:

- Glucocoticoids mainly increase bone resorption by enhancing the differentiation and maturation of osteoclasts. Glucocorticoids also inhibit osteoblastogenesis and promote apoptosis of osteoblasts and osteocytes resulting in decreased bone formation during long-term use.
- Corticosteroids reduce intestinal calcium absorption by antagonizing vitamin D action and increase renal calcium excretion. This may contribute to secondary hyperparathyroidism and bone loss.
- In some patients corticosteroids also reduce gonadal function, which may further contribute to bone fragility.

Qh. What are the preventive measures for osteoporosis in patients treated with glucocorticoids?

The preventive measures for osteoporosis in patients treated with glucocorticoids are:

1. Non-pharmacological management (such as nutrition and exercise) should be advocated in all patients receiving long-term glucocorticoid treatment.
2. Using the minimally effective dose and duration of glucocorticoid should be considered.
3. Pharmacological anti-osteoporotic treatment is recommended in patients at high risk of fracture; anti-resorptives are the primary option but anabolic therapy might also be considered.

Qi. What is the underlying mechanism for the rise in blood pressure in a patient treated with hydrocortisone and fludrocortisone?

Corticosteroids with strong mineralocorticoid effects, such as fludrocortisone and hydrocortisone cause greatest amount of sodium and water retention. Overstimulation of the mineralocorticoid receptor results in sodium retention in the kidney leading to volume expansion and a subsequent increase in blood pressure. Increased vascular smooth muscle responsiveness to adrenaline may also contribute to pressor response. Other mechanisms that raise blood pressure include structural changes of the vascular wall, electrolyte changes, alterations in sodium–potassium pump activity and permeability.

CASE 2: STEROIDS IN THE TREATMENT OF EYE DISEASE

A 50-year-old male patient 'CD' presented to the ophthalmology OPD with pain and redness in the eye. On examination, episcleral vessels were diffusely injected and the episclera was thickened inferiorly. His blood pressure was 140/90 mm of Hg.

Your diagnosis: **Episcleritis**

Treatment prescribed was 0.1% dexamethasone sodium phosphate solution, 2 drops in the conjunctival sac for 2 weeks and then follow-up.

Qa. Among glucocorticoids, why is dexamethasone preferred over prednisolone or hydrocortisone in the treatment of episcleritis in case of CD?

Hydrocortisone is short acting, has equal degree of glucocorticoid and mineralocorticoid actions and therefore produces anti-inflammatory effect accompanied by salt and water retention which is undesirable in the treatment of episcleritis.

Prednisolone is intermediate acting, produces greater anti-inflammatory effect than hydrocortisone with little salt retention capacity.

Dexamethasone is long acting and the anti-inflammatory effect is of greater magnitude than prednisolone with no salt retention capacity.

Therefore, dexamethasone is preferred over prednisolone or hydrocortisone in the treatment of inflammatory condition such as episcleritis.

Qb. Explain why intraocular pressure should be monitored when glucocorticoids are applied to the eye for more than 2 weeks.

Topical glucocorticoid therapy frequently *increases intraocular pressure* in normal eyes and exacerbates intraocular hypertension in patients with pre-existing glaucoma. Therefore, intraocular pressure should be monitored when glucocorticoids are applied to the eye for more than 2 weeks.

Qc. What is the risk if glucocorticoids are administered for the treatment of herpes simplex keratitis and lacerations in the eye?

In herpes simplex keratitis, glucocorticoids cause symptomatic relief and can mask evidence of progression of the infection until sight is irreversibly lost.

In the treatment of mechanical lacerations, glucocorticoids delay wound healing and promote the development and spread of infection.

Therefore, glucocorticoids are not used in herpes simplex keratitis and lacerations of the eye.

Qd. Which are the other ophthalmic conditions where corticosteroids are used? Which steroids are preferred for ophthalmic purpose?

Steroids are used in eye diseases with associated inflammation that include allergic conjunctivitis, iritis, iridocyclitis, external eye inflammatory disease, postoperative inflammation following refractive, corneal and intraocular surgery, a variety of retinal conditions including diabetic retinopathy, cystoid macular edema and optic neuritis.

The steroids which are used for ophthalmic purpose include hydrocortisone, prednisolone, dexamethasone, fluorometholone or medrysone in various ophthalmic preparations.

CASE 3: ROLE OF GLUCOCORTICOIDS AS ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE AGENTS

RY, a 55-year-old female with symptoms of joint pain and swelling for last 1 year, difficulty in walking, increased knee pain for 3–4 months. Her laboratory investigations revealed rheumatoid arthritis.

Qa. How do glucocorticoids play a role in suppressing inflammation and the immune system in rheumatoid arthritis as in RY?

Glucocorticoids induce the production of lipocortin which inhibits phospholipase A2 and subsequently decreased production of arachidonic acid metabolites such as prostaglandins, leukotrienes and platelet activating factor which mediate inflammation.

Glucocorticoids repress transcription of many genes encoding pro-inflammatory cytokines and chemokines, cell adhesion molecules and key enzymes involved in the initiation and/or maintenance of the host inflammatory response.

- They inhibit the synthesis of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) which act as signalling molecules in the process of inflammation and cause vasodilation, increased capillary permeability and leukocyte emigration into the injured site.
- They inhibit the synthesis of chemokines, i.e. IL-8 and decrease the expression of chemokine receptor and adhesion molecules which in turn reduce the migration and recruitment of leukocytes to the inflammatory sites.
- Glucocorticoids decrease the synthesis of TNF-α that can cause cell death or apoptosis.

The reduced production of IL-2 produces the following immunosuppressive and anti-inflammatory effects:

- Inhibits T cell proliferation and decreases cytokine production (IL-4, IFN-ϒ)
- Inhibits β cell proliferation and antibody production
- Inhibits natural killer cell proliferation and decreases cytolytic activity.

Case Continued

RY was prescribed 5 mg of prednisolone twice daily for a week. RY continued to take the medication for 2 months for better improvement of symptoms and discontinued suddenly. She was brought to the emergency with complaints of nausea, vomiting, muscle pain, tiredness and dizziness.

She was diagnosed with acute adrenocortical insufficiency.

Q1a. What is the likely cause for acute adrenocortical insufficiency in patient RY?

Acute adrenal insufficiency may result from abrupt withdrawal of glucocorticoids used at high doses or for prolonged period. There is suppression of hypothalamic-pituitary-axis induced by exogenous glucocorticoid administration. So, abruptly stopping prednisolone can cause withdrawal symptoms as manifested by RY.

Qb. What is the immediate management of acute adrenocortical insufficiency in RY?

AB can be managed in the following manner:

- An initial intravenous bolus of 100 mg, hydrocortisone hemisuccinate should be given followed by continuous infusion at a rate of 50–100 mg every 8 hours.
- Dextrose in normal saline in adequate amounts should be administered.
- Vasopressor drugs to maintain blood pressure can be used.
- Appropriate therapy for precipitating causes such as infection, trauma or haemorrhage must be considered.

Following recovery, 4th–5th day onwards, hydrocortisone is given orally in maintenance doses (25–30 mg/day), together with 9-alpha-fluorohydrocortisone.

Qc. Although acute adrenal insufficiency is characterized by both glucocorticoid and mineralocorticoid deficiency, only hydrocortisone, a glucocorticoid is administered and no mineralocorticoid was administered. Explain why?

Although acute adrenal insufficiency leads to deficiency of both mineralocorticoid and glucocorticoid, only glucocorticoid, that is, hydrocortisone is given in 100 mg IV bolus dose followed by continuous IV infusion at a rate of 50–100 mg every 8 hours. This dose confers sufficient mineralocorticoid activity, so mineralocorticoid replacement is not needed separately.

Qd. What precautions should be taken, if the patient is to be given pharmacological doses of hydrocortisone for a prolonged period?

- Glucocorticoid-induced HPA axis hypofunction depends on the duration and dosage of exogenous glucocorticoid administration. Hence, use of minimum effective dose and duration of glucocorticoid should be considered. Alternate day therapy also may be considered.
- The timing of steroid administration may affect the degree of adrenal suppression. Higher dose of steroids at night time will produce more marked HPA suppression because higher doses block early morning ACTH surge. Also tissue sensitivity to glucocorticoid is increased in the evening and early night hours. Hence, lower dose in the evening and higher dose in morning is appropriate for therapeutic purpose.
- Abrupt withdrawal of corticosteroid after prolonged use should be avoided as it may precipitate adrenal insufficiency. Withdrawal should be done gradually by tapering the dose.
- In case of infection/trauma/stress, there is activation of HPA axis with ACTH-driven increased cortisol secretion leading to marked increase in plasma concentration of cortisol. Hence, dose of steroid should be increased to meet the needs of increased demand in such situations.

CASE 4: USE OF STEROIDS IN SKIN DISEASES

MN, a 25-year-old male, working in metal manufacturing industry developed rash characterized by pruritic papules and vesicles on an erythematous base, on the hands and lower arms. The skin problem started a few days after the exposure to his workplace. This was diagnosed as acute allergic contact dermatitis.

The rash resolved on applying ointment clobetasol propionate on the affected areas twice daily for 4 weeks.

Qa. Enumerate some of the topical available preparations of corticosteroids. How do corticosteroids play a role in the treatment of various skin diseases?

Topical preparations of steroids include betamethasone dipropionate, clobetasol propionate, amcinonide, fluocinolone acetonide, hydrocortisone valerate, triamcinolone acetonide, mometasone furoate, dexamethasone sodium phosphate.

Corticosteroids are used in the treatment of various skin disorders by acting through anti-inflammatory, anti-mitotic and immunosuppressive effects.

CASE 5: STEROIDS DURING LATE PRETERM LABOR

TN, a young 27-year-old pregnant female at 30 weeks of gestation, complains of sudden onset of lower abdomen pain and uterine contractions and has a feeling of 'sudden gush of water'. She was rushed to the hospital for appropriate management.

Qa. Given that TN is in preterm labor at 30 weeks' gestation, what medications can be given to help facilitate fetal lung maturation?

Betamethasone or dexamethasone should be administered for all women in preterm labor between 24 and 34 weeks' gestation. TN should be given betamethasone 12 mg intramuscularly now and a second dose 24 hours later to facilitate fetal lung maturation by increasing production of fetal lung surfactant, thereby reducing the incidence and severity of respiratory distress syndrome.

Antenatal corticosteroid administration (betamethasone and dexamethasone) also decreases the incidence of intraventricular haemorrhage, necrotizing enterocolitis, and neonatal death.

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Section

V

Neurologic Disorders

12. Sedatives and Hypnotics
13. Antiparkinsonian Drugs
14. Antiepileptics
15. Antidepressant Drugs
16. Antipsychotic Drugs

Chapter

12

Sedatives and Hypnotics

CASE 1: DRUG THERAPY FOR SLEEP ONSET INSOMNIA

Mr RX usually goes to bed at 10 pm, takes 2 to 3 hours to fall asleep, wakes-up late in the morning, 9:30 am past and has to hurry up to office. He drives to his workplace and is currently working on a project in which he has a leadership role to play. He consults his physician regarding his difficulty in initiating sleep which is affecting his work schedule.

Qa. Define sedatives and hypnotics. Mention the distinction between sedatives and hypnotics.

Sedatives are drugs that decrease activity and have a calming, relaxing effect without inducing sleep but at higher doses, sedatives usually cause sleep.

Hypnotics are drugs used mainly to cause sleep. Therefore, there is no clear distinction between sedatives and hypnotics.

Qb. How does sleep move through different stages in a continuous cycle? What is the importance of each stage of sleep cycle?

NREM sleep (75 to 80%)

Stages	*Time spent*	*Changes*	*Functions*
Stage 1	2% to 5% of sleep time	Relaxed wakefulness	Helps to initiate sleep
Stage 2	50% of sleep time	Lighter sleep rapid onset sleep (theta wave)	Provides rest for the muscles and brain
Stage 3	5% of sleep time	Deep sleep slow wave sleep (delta wave)	Body repairs and regenerates tissues, builds bone and muscle and appears to strengthen the immune system
Stage 4	10% to 15% of sleep time	Deep sleep Slow wave sleep (delta wave)	

Stage	*Time spent*	*Function*
REM sleep	20% to 25% of sleep time	Consolidation of learning

Qc. Mention the effects of sedatives and hypnotics on different stages of sleep cycle.

The sedative and hypnotic drugs affect different stages of sleep cycle in the following ways:

- Stage 2 of NREM sleep is prolonged resulting in increase in total sleep duration.
- Decrease time spent in REM sleep. This effect is maximum with barbiturates, minimum with Z compounds and intermediate with benzodiazepines.
- Decrease stages 3 and 4 of NREM sleep.

Qd. Enumerate the different classes of sedative/hypnotic drugs available.

Sedative/hypnotic drug products are broadly classified as follows:

Benzodiazepines

Short-acting

Triazolam, oxazepam, midazolam

Intermediate-acting

Alprazolam, estazolam, temazepam, lorazepam, nitrazepam

Long-acting

Diazepam, flurazepam, clonazepam, chlordiazepoxide

Non-benzodiazepine drugs (NBRA drugs; also known as Z hypnotics)

Zolpidem, zaleplon, zopiclone, eszopiclone

Barbiturates

Long-acting

Phenobarbital, mephobarbital

Short-acting

Hexobarbitone, pentobarbitone

Ultrashort-acting

Thiopental, methohexital

Qe. Mention the characteristics of an ideal hypnotic.

The characteristics of an ideal hypnotic are:

- Rapid onset of action (within 20 min, the natural time to fall asleep)
- Less nocturnal awakenings and helps the patient to sleep throughout the night.
- Does not cause daytime sedation
- Causes no tolerance or abuse potential

Qf. Which sedatives would be appropriate for the treatment of insomnia in RX?

Mr RX has trouble in *initiating sleep but has no problem in maintaining continuous sleep*. He wishes to take medication which will help him to fall asleep as well as avoid next day hangover effects of the drug so that he can meet his job obligations. A rapid-acting hypnotic with short half-life and few adverse effects is desirable. In case of Mr RX, zolpidem, zaleplon, zopiclone, eszopiclone also known as Z drugs or a short-acting BZD (e.g. triazolam) is a reasonable option.

Qg. Explain why Z drugs are preferred over benzodiazepines for the treatment of insomnia, as in case of Mr RX.

In case of Mr RX, 'Z drugs' are preferred over benzodiazepines for the treatment of insomnia for the following reasons:

- Z drugs have rapid onset of action and highly effective in inducing sleep.
- They have short duration of action and hence less likely to produce residual daytime sedation.
- There is minimal alteration of physiological sleep architecture including REM sleep and therefore lower rates of REM rebound (vivid dreams, increased autonomic instability) and rebound insomnia (insomnia getting worse than before) on discontinuation.
- Z drugs have least effect on memory and cognitive function.
- Z drugs are less likely to produce tolerance and dependence as compared with BZDs. Withdrawal symptoms are not common with these drugs.

CASE 2: DRUG THERAPY FOR CHRONIC INSOMNIA

A 55-year-old man MN who lost his job approximately 5 months ago, complains of difficulty in sleeping at night and has early morning awakenings. He recently found a new job but has continued to experience difficulty in sleeping. He reports that he falls asleep more easily while watching television early in the evening and feels sleepy outside the house. He is preoccupied with his inability to sleep at night. General physical examination and routine laboratory screening are unremarkable. He denies the use of alcohol, coffee and other drugs.

MN was prescribed tab. temazepam 15 mg at bedtime for a brief period.

Qa. Explain the pharmacokinetic properties of benzodiazepine that determine drug action and how do they influence selection of drug for the treatment of insomnia.

The benzodiazepines differ in their pharmacokinetic characteristics that determine drug action. The pharmacokinetic properties include lipopilicity, elimination half-life and hepatic clearance.

1. Lipophilicity

Lipid soluble drugs easily penetrate through cell membranes and have rapid onset of action. Highly lipophilic benzodiazepine agents are also quickly redistributed out of the brain which decreases the duration of action acutely.

2. Elimination half-life

Drugs with *short half-life* are effective in treating individuals who have difficulty in going to sleep but lack the ability maintain continuous sleep. These drugs are unlikely to cause daytime impairment.

Drugs with *intermediate and long elimination half-life* are mainly used for sleep maintenance. Almost all have potential for hangover effects and cause daytime sedation. It is important to note that drugs with long half-life are less likely to produce withdrawal symptoms.

3. Hepatic metabolism

Many of the benzodiazepines form phase I active metabolites, which prolong the half-life of the parent drug and leads to extension of the pharmacological effects of the drug. There can also be accumulation on multiple dosing. Examples of these drugs include midazolam (active metabolite, hydroxymethyl midazolam), diazepam (active metabolite oxazepam), flurazepam (active metabolite desmethylflurazepam), chlordiazepoxide (active metabolite desmethyldiazepam) alprazolam (active metabolite, alfa-hydroxyalprazolam).

Lorazepam, oxazepam and temazepam do not form active metabolites and are metabolised by conjugation reaction to form water soluble metabolites and excreted in urine. They are unlikely to accumulate with chronic administration and are preferred over longer acting agents in patients with liver disease and in elderly.

Qb. Given that, MN is a case of chronic insomnia. Why do you think temazepam, a benzodiazepine agent, was prescribed instead of Z drugs?

This is a case of chronic insomnia since the duration of sleep disorder is more than 3 weeks. Insomnia is severe because there is difficulty in falling asleep, difficulty in maintaining sleep followed by early morning awakening and excessive daytime sleepiness.

Z drugs are effective in inducing sleep but may not help in maintaining sleep throughout the night. Temazepam, a benzodiazepine agent, has moderate lipid solubility and takes 1 to 2 hours to induce sleep. It does not undergo hepatic oxidative metabolism to form active metabolites and is less likely to accumulate with multiple dosing. Temazepam has an intermediate duration of action of 8–12 hours and there is less potential for daytime impairment.

Qc. The patient is curious to know the long-term effects of benzodiazepines and how these effects can be avoided or minimized?

During counselling, the patient was made aware of the long-term effects of benzodiazepines which are the following:

1. **Tolerance:** When benzodiazepine is used for a prolonged period, there is reduction in effectiveness of a repeated given dose or a higher dose of the drug is required to produce the same response. So, the patient 'MN' may develop tolerance within days or weeks of taking treatment and there is a chance that he may not respond to the drug any further or may require a higher dose of drug to treat his insomnia.
2. **Dependence:** The hallmark of physical dependence is withdrawal symptoms. If benzodiazepine is abruptly stopped after 7 to 10 days of continued use there can be rebound insomnia (insomnia worse than before).
3. **Drug–drug interaction** is an important consideration related to the use of benzodiazepines. Cytochrome P450 enzymes catalyzing oxidative metabolism, are involved in the metabolism of many of the benzodiazepines. Concurrent administration of drugs which are inhibitors of CYP3A4 enzymes, increase the plasma concentration of benzodiazepine, leading to untoward effects associated with benzodiazepines.
4. **Other disadvantages of benzodiazepine** include impairment in new learning and daytime functioning.

The patient should be advised to avoid sudden discontinuation of benzodiazepines and gradual reduction in dose should be under the supervision of the physician.

Case Continued

The patient 'MN' inquires his doctor about any new sleep medications available for the treatment of insomnia.

Qa. What are the newer treatment alternatives to benzodiazepine and non-benzodiazepine drugs? How do these drugs work in the management of insomnia?

Current and emerging therapies for insomnia are suvorexant and ramelteon.

1. ***Suvorexant*** is a selective antagonist of orexin receptors (OX1R and OX2R) which are responsible for wakefulness and is useful in the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Most commonly reported adverse effect is daytime somnolence.
2. ***Ramelteon*** is a melatonin receptor agonist having activity at MT1 and MT2 receptors that contributes to sleep promoting properties similar to the actions produced by endogenous melatonin involved in the maintenance of the circadian rhythm underlying the normal sleep wake cycle. It speeds up the onset of sleep and increases the total sleep time. It is shown to have no action on $GABA_A$ receptors which are associated with anxiolytic, myorelaxant and amnestic effects. It has no potential for drug abuse, dependence and withdrawal.

Qb. Benzodiazepines are used in wide range of uses besides treatment of insomnia whereas Z group of drugs are primarily used as hypnotics. Explain why.

Benzodiazepines have *non-selective action on* $GABA_A$ *receptors* and interact with various subunits of $GABA_A$ receptors and hence show pharmacologic properties including sedation, anxiolytic and muscle relaxant effect, and anterograde amnesia. Therefore, in addition to the treatment of insomnia benzodiazepines are used as:

- Treatment for panic disorder and anxiety neurosis
- Adjuncts to selective serotonin reuptake inhibitors for treatment of obsessive compulsive disorder
- Adjuncts to antipsychotics for treatment of acute mania or agitation
- Preanaesthetic medication or induction of anaesthesia.
- Anticonvulsant for treating seizure disorders.
- Treatment for alcohol withdrawal syndrome.

Non-benzodiazepine drugs (NBRA; also known as Z hypnotics) have *selective activity at the α1-subunit of the* $GABA_A$ *receptor* which imparts hypnotic efficacy. They lack anxiolytic and muscle relaxant effect, and do not cause anterograde amnesia. They are only used as sedatives and hypnotics and have no other therapeutic uses.

Qc. Mention the benzodiazepines that are commonly used as preanaesthetic medications and induction of anaesthesia. Explain the rationale for their use in this condition.

- Diazepam, lorazepam and midazolam are available as IV formulations and widely used as preanaesthetic medications and induction of anaesthesia. They produce their action by enhancing GABA inhibition by binding to the benzodiazepine GABA receptor.
- These agents have high lipid solubilities and hence rapidly cross the blood–brain barrier to produce quick onset of action which is desirable to produce the effects of anaesthesia.
- Highly lipophilic benzodiazepine agents are quickly redistributed out of the brain which decreases the duration of action acutely and therefore used for induction of preoperative sedation and anxiolysis.

Qd. How do benzodiazepines play a role in the treatment of alcohol withdrawal syndrome?

Chronic exposure to alcohol have the potential for abuse and dependence. Abstinence from alcohol in these cases result in withdrawal symptoms due to increased sympathetic nervous system response and sometimes seizures which may be life-threatening. Administration of a long-acting benzodiazepine (such as diazepam) suppresses CNS hyperactivity and activity of the sympathetic nervous system. Long-acting BZD agents are preferred as they are less likely to cause withdrawal symptoms than short-acting or intermediate-acting agents.

Qe. Compare the effects of benzodiazepines (BZDs) and barbiturates, used as sedatives/hypnotics for sleep disorders. Why diazepam is preferred over phenobarbital as sedative-hypnotic drug?

1. Both barbiturates and benzodiazepines are modulators of $GABA_A$ receptor and potentiate GABA-mediated Cl^- current hyperpolarization. This accounts for GABA inhibitory effect throughout the central nervous system. Barbiturates bind to $GABA_A$ receptor at a site within a pocket formed by the interfaces of *α- and β-subunits* and benzodiazepines bind to BZD binding site formed by *α- and γ-subunits* of $GABA_A$ receptor.
2. Barbiturates increase the *duration of chloride channel opening* while BZD increases the *frequency of channel opening*. Both barbiturates and benzodiazepines have GABA facilitatory action but at higher doses *barbiturates exhibit GABA mimetic effect* and directly increase chloride ion conductance. Thus, barbiturates are more potent than BZDs and produce more pronounced CNS depressant actions.
3. The alteration in normal sleep architecture is more with barbiturates and less with benzodiazepines. The rebound increase in REM sleep duration with bad dreams and nightmares is commonly seen with barbiturates than BZDs and is distressing. The sedative actions of barbiturates is considerably higher than BZDs, producing next day hangover and daytime sleepiness which might be troublesome.
4. Barbiturates are commonly used therapeutically for anaesthesia and control of epilepsy while BZDs are highly effective in treating anxiety and insomnia due to sleep inducing, sedative and muscle-relaxing properties.
5. BZDs develop tolerance and dependence more slowly and their liability for abuse is lower than that of the barbiturates.
6. Barbiturates have a low therapeutic index and are more likely to increase the risk of serious complications such as overdose, respiratory failure and death. While BZDs have higher safety margin and chances of side effects are less.
7. BZD overdose can be treated with flumazenil, a BZD receptor antagonist whereas there is no specific antidote for barbiturate overdose.

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Chapter

13

Antiparkinsonian Drugs

CASE 1: DRUG THERAPY FOR PARKINSON'S DISEASE

Mr 'RK', a 47-year-old man, professor in a college attends neurology clinic with complaints of rest tremor of the right hand and arm and difficulty in writing because of unsteadiness in his right hand. He has no difficulty in driving to his workplace. His wife notices that he moves slowly and has a diminished range of facial expressions. He has no postural abnormalities. His speech is slow and monotonous. On physical examination, the doctor finds that Mr 'RK' has increased tone and rigidity in the upper extremity, particularly on the right side. The remainder of his physical examination is within normal limits. All laboratory tests are normal including liver function tests and kidney function tests.

Mr 'RK' is diagnosed to be suffering from early stages of Parkinson's disease.

Treatment was initiated with pramipexole, a dopamine agonist at a dosage of 0.5 mg three times in a day and the patient responded well to treatment.

Qa. How do the clinical features relate to the pathophysiological changes in Parkinson's disease?

The classic features of Parkinson's disease are bradykinesia, limb rigidity and tremor. This is due to the following pathophysiological changes in Parkinson's disease.

- Loss of dopaminergic neurons in the nigrostriatal tracts of the brain which contains about 80% of brain's dopamine and is involved in maintaining muscle tone and posture.
- Progressive dopamine depletion leads to disinhibition of acetylcholine neurons due to loss of dopamine-mediated inhibition of acetylcholine neurons. This results in relative increase in cholinergic activity manifesting as tremor.

Qb. What will be your therapeutic objective? What are the treatment strategies to control the signs and symptoms of Parkinson's disease?

The therapeutic objective is to replenish the supply of dopamine which is reduced due to degeneration of dopaminergic neurons in the brain or to reduce the cholinergic hyperactivity.

The following treatment strategies can be used to control the signs and symptoms of Parkinson's disease:

- Administering levodopa, an immediate precursor of dopamine.
- Using dopamine agonists (e.g. pramipexole, ropinirole) to directly stimulate the postsynaptic dopamine receptors within the striatum.

- Inhibition of dopamine breakdown through use of MAO-B inhibitors (e.g. selegiline, rasagiline) or COMT inhibitors (e.g. entacapone).
- Anticholinergics efficacious for cholinergic-mediated tremor and in drug-induced parkinsonism.

Qc. Given that RK is a 47-year-old man, diagnosed with Parkinson's disease which is early in onset, why do you think, pramipexole is preferred over levodopa in the management of his condition?

Patients with younger age at disease onset, milder form of disease with moderate functional impairment such as 'RK' are good candidates for initial therapy with pramipexole, a dopamine agonist.

- Starting dopamine agonists in the early stages of disease delays the need for levodopa and the onset of levodopa-induced dyskinesias. This is because, although levodopa is the most effective therapy in Parkinson's disease, with continued use, tolerance to the drug may develop and the efficacy of levodopa decreases. This increases the risk of motor complications and dyskinesias. Escalating the doses of levodopa increases the risk of undesirable side effects.
- Dopamine agonists are more likely to cause CNS adverse effects such as confusion, dizziness, hallucinations, sleep disturbances which might be intolerable for older patients as they are more susceptible to hallucinatory and cognitive problems. In younger patients these drugs may be used with caution.
- Long elimination half-life of dopamine agonists compared to levodopa allows less frequent dosing and more sustained action and therefore less likely to induce 'off' periods.
- The availability of dopamine agonist in the CNS is not affected by protein meal unlike the levels of levodopa which is compromised in presence of circulating amino acids.

Therefore, in young patients who are likely to live for many years with Parkinson's disease and have high lifetime risk of developing motor complications, pramipexole, a dopamine agonist is preferred as initial therapy and levodopa reserved for advanced stages of disease and in older patients.

Qd. Inflammation and oxidative stress have been shown to play an essential role in Parkinson's disease. How do the dopamine agonists prevent free radical-induced neuronal damage and are better than levodopa?

Dopamine (DA) is a source of reactive oxygen species (ROS) in the CNS. In patients with Parkinson's disease, there is an excess amount of cytosolic DA outside of the synaptic vesicles due to damaged neurons with impaired uptake. Chronic levodopa treatment may result in an excess amount of cytosolic DA which is unstable and undergoes auto-oxidation to form free radicals that may contribute to neurodegeneration.

Dopamine agonists directly stimulate the dopaminergic receptors, acting independent of the degenerating dopaminergic neurons, do not require metabolic conversion to dopamine and does not involve metabolic degradation of dopamine and free radical formation thus delaying the neurodegenerative process. Therefore they are considered to be better than levodopa, in preventing free radical-induced neuronal damage.

Qe. List the dopamine agonists that can be used in the treatment of Parkinson's disease. Why dopamine agonists of 2nd generation are preferred over 1st generation in the treatment of Parkinson's disease?

There are two generations of dopamine agonists:

- 1st generation (ergot derivatives): Bromocriptine, cabergoline and pergolide
- 2nd generation (non-ergot derivatives): Pramipexole, ropinirole and rotigotine

Adverse effects such as nausea, vomiting, postural hypotension and peripheral edema are predominantly seen with the 1st generation agents. The older agents are now rarely used because of increased risk of retroperitoneal, pleural, and pericardial fibrosis as well as a two-to-fourfold increased risk for cardiac valve fibrosis.

Pramipexole and ropinirole have selective action on D2 receptors without any significant affinity for D1 receptors. Stimulation of D2 receptor is responsible for reducing rigidity and bradykinesia and useful in treating symptoms of Parkinson's disease, with reduced risk of side effects.

Therefore, pramipexole and ropinirole are preferred drugs, used as initial therapy in the treatment of patients with parkinsonism.

Qf. Should pramipexole be prescribed in a patient of parkinsonism with associated kidney disease? If not, give reasons. What is the safer alternative to pramipexole?

Pramipexole should be prescribed in patients with normal renal function because the excretion of the drug is primarily through the kidney. So, renal dysfunction can lead to drug accumulation and toxicity. In contrast, ropinirole is metabolized by the liver so no dose adjustment is required in renal failure and can safely be administered in renal disease.

Qg. In which formulation is rotigotine available and how is it advantageous for the patient of Parkinson's disease?

Rotigotine is a non-ergot dopamine receptor agonist that is formulated in a transdermal patch delivery system designed for once-a-day application.

The transdermal patch delivery system allows slow and continuous release of the drug allowing more sustained action on dopamine receptors reducing the frequency of administration and increasing adherence. It is also useful for those who have difficulty in swallowing.

Qh. Considering that the patient 'RK', drives to his workplace, what advice would you give to 'RK' who is on treatment with pramipexole?

Dopamine agonists such as pramipexole have been reported to cause sudden excessive daytime sleepiness or feeling of drowsiness which could result in accidents while driving. Therefore, patients on pramipexole should be advised to avoid driving or engage themselves in potentially dangerous activities. He should report to the health care practitioner, if there is excessive unsteadiness or dizziness.

Case Continued

Over a period of 7 years, his treatment has been modified to include rasagiline, a MAO-B inhibitor in addition to pramipexole to have smooth control over his symptoms.

Qa. How does rasagiline work? How is it beneficial in Parkinson's disease (PD)?

Rasagiline blocks degradation of dopamine through inhibition of MAO-B enzyme in the brain thereby increasing the levels of dopamine and producing therapeutic effect in PD.

MAO-B inhibitors by inhibiting the catabolism of dopamine, prevent the generation of toxic-free radicals, which accelerate the neurodegenerative process. This accounts for neuroprotective effect of rasagiline. This is useful in the early stages of PD when the disease is mild, as monotherapy or as an adjunct to delay, the progress of the disease and prevent 'On–off 'episodes or onset of dyskinesias.

Qb. How is rasagiline better than selegiline in the treatment of Parkinson's disease?

Selegiline forms metabolites which include amphetamine and methamphetamine that may cause anxiety, insomnia and other adverse symptoms. Unlike selegiline, rasagiline does not give rise to undesirable amphetamine metabolites and therefore has a better side effect profile.

Qc. Why selective MAO-B inhibitors are preferred over non-selective MAO inhibitors in the treatment of Parkinsonism?

At clinically recommended doses, selegiline is a selective inhibitor of MAO-B which is predominantly present in the striatum and is responsible for metabolic breakdown of dopamine in the brain. It has no significant action on the catecholamines in the periphery. In contrast, non-selective MAO inhibitors exert inhibitory effect on the metabolism of catecholamines in the periphery raising their levels. Ingestion of tyramine containing food such as cheese, wine, etc. could potentiate catecholamine action due to the indirect sympathomimetic effect of tyramine giving rise to cheese reaction or hypertensive crisis.

Case Continued

In past 2 weeks, there is gradual worsening of parkinsonian symptoms and his wife notices the postural changes. RK has a stooped posture and is not showing adequate response to the given treatment and goes to the neurologist for further consultation.

Therapy was initiated with immediate release of carbidopa/levodopa 25 mg/100 mg three times a day in addition to previous medications, pramipexole and rasagiline. Over a period of time, the dose of levodopa was titrated slowly with close monitoring of the RK and he was maintained on carbidopa/levodopa 25 mg/250 mg 4 times a day. There was dramatic improvement in symptoms and his day-to-day functioning improved.

Qa. Explain the rationale for combining carbidopa with levodopa. What are the advantages of the combination?

Levodopa, a precursor of dopamine, gets converted into active dopamine in presence of the enzyme dopa decarboxylase of the gastrointestinal tract and peripheral tissues. Dopamine itself cannot penetrate the blood–brain barrier. This results in decreased availability of dopamine in the brain and is associated with peripheral side effects.

Carbidopa is an inhibitor of dopa-decarboxylase enzyme, produces action mainly at the periphery and does not cross the blood–brain barrier. Inhibition of dopa decarboxylase enzyme at the periphery increases the plasma levels of levodopa which freely passes through the blood–brain barrier and enters the brain, where it gets converted to dopamine by dopa decarboxylase (DDC) of the brain and is available for action.

For this reason, levodopa is always coadministered with a dopamine decarboxylase inhibitor. The combination offers the following advantages:

- Prolongs half-life of levodopa, thus reduces dose by 75%.
- Peripheral side effects are reduced viz. nausea, vomiting, cardiac complications.
- On–off effect is minimized since dopamine level is more sustained in the brain.
- Improvement is faster.

Qb. What are the common adverse effects associated with levodopa use in Parkinson's disease?

Most common side effects are gastrointestinal side effects such as nausea, vomiting and anorexia due to CTZ stimulation with dopamine. In cardiovascular side effects, postural hypotension is seen due to the release of dopamine into the circulation. Cardiac arrhythmias can occur in 10% of the patients. Similar to dopamine agonists, levodopa is also known to cause CNS side effects such as confusion, psychosis, vivid dreams and other mental disturbances but at lower rates compared with dopamine agonists.

Qc. Explain how ingestion of protein meal modifies clinical response to levodopa. What dietary instructions should be given by the physician to improve the efficacy of levodopa?

Levodopa is actively transported across the blood–brain barrier by neutral amino acid transporter system, which also facilitates the transport of neutral amino acids such as L-leucine, L-valine, L-isoleucine, L-phenylalanine. Levodopa when administered in presence of protein meal, the neutral amino acids compete with levodopa for transport into the brain and high plasma concentrations of these amino acids may decrease the concentrations of levodopa in the brain.

Patients should be instructed to take immediate-release carbidopa/levodopa 30 minutes before or 60 minutes after meals for optimal efficacy. Intake of low protein meal should be encouraged.

Case Continued

After 3 years, RK is gradually experiencing frequent episodes of involuntary movements of the face and irregular jerky movements of the trunk lasting for few minutes. There are also periods of freezing when he is not able to move his body. On consultation, the physician adjusted the dose and frequency of levodopa which provided comfort to the patient RK.

Qa. What could be the possible explanation for the development of abnormal movements described above, in case of patient RK?

As the disease advances, there are fluctuations in motor functions characterised by episodes of increased rigidity and stiffness usually in their shoulders, arm and leg muscles which prevents mobility. This is known as akinetic state or 'off' phenomenon and is linked to decline in the plasma levels of levodopa. This can be managed by increasing the dose of levodopa and the frequency of dosing of the medication.

Off time is followed by 'on' periods characterised by normal or dyskinetic movements which manifest as uncontrollable rhythmic movements of head and trunk. Dyskinesias are due to sudden delivery of high concentrations of dopamine into the striatum which usually occurs at peak dose levels of levodopa resulting in increased dopaminergic activity. Dyskinesias can be controlled by taking smaller doses of levodopa although this may increase the likelihood of 'off' periods.

Thus, as the disease advances, an increase in motor fluctuations is observed and managing the symptoms by adjusting the dose and frequency of dopaminergic drugs so as to maximize the beneficial effect while minimizing the undesirable side effects becomes a challenge.

Qb. The patient RK reports that he has experienced moments of immobility and could not rise from his bed particularly in the morning. The discomfort was relieved immediately after taking his levodopa dose. What could be the possible reason for the above complaint?

The symptoms reported by RK are due to the wearing-off effect of dopaminergic drugs which means decreased therapeutic effect of the drug towards the latter part of dosing interval resulting in symptoms of immobility. This is particularly seen with levodopa therapy because the elimination half-life of levodopa is about 1.5 hours, so much of the effect from the evening dose of levodopa will dissipate by morning and hence the episodes of freezing are observed particularly in the morning and is alleviated shortly after taking the morning dose of levodopa.

Wearing off can be improved by various means such as shortening the dosing interval or with the addition of adjunctive therapy (if not already present) with a dopamine agonist, MAO-B inhibitor or levodopa extender such as a COMT inhibitor.

Qc. How does progression of Parkinson's disease contribute to accentuation of motor complications?

As the disease advances, there is progressive degeneration of dopaminergic nerve terminals reducing the ability to presynaptically store dopamine and release into the synaptic cleft leading to incomplete delivery of dopamine in the striatum. As a result, the dopamine receptors are subjected to intermittent, pulsatile stimulation rather than a more physiologic tonic stimulation.

Overactivity of excitatory pathways mediated by neurotransmitters such as glutamate may also be involved.

Qd. What is the role of COMT inhibitors in the management of Parkinson's disease and how do they act? Why is entacapone preferred over tolcapone in the treatment of Parkinson's disease?

COMT inhibitors inhibit the peripheral degradation of levodopa thereby increasing the levels of levodopa available for transport into the brain. This prolongs the therapeutic effect of levodopa, reduces on–off phenomenon associated with levodopa and is used as an add-on therapy with levodopa.

Both entacapone and tolcapone are COMT inhibitors. Tolcapone has central as well as peripheral action and is long acting whereas entacapone acts only peripherally and is short-acting. However, the use of tolcapone is limited, due to increased risk for hepatotoxicity. Entacapone is safer as compared to tolcapone and is commonly used in the treatment of PD.

Qe. Is amantadine, an antiviral drug, useful in the treatment of Parkinson's disease (PD)? If yes, give the pharmacological basis for the use of amantadine in the treatment of PD.

Amantadine, although an antiviral drug, is found to relieve the symptoms of parkinsonism and is particularly useful in the management of levodopa-induced dyskinesias in terms of duration and severity.

Amantadine acts through the following mechanisms that contribute in the treatment of Parkinson's disease:

- Amantadine inhibits the reuptake of dopamine into the nerve terminals and also augments the release of dopamine thereby raising the concentrations of dopamine in the synaptic cleft.
- It is reported to possess antimuscarinic action which may reduce cholinergic hyperactivity in PD.
- It acts as an antagonist at NMDA receptor and thus inhibits glutamate-mediated excitation implicated in the pathophysiology of dyskinesias.

CASE 2: DRUG-INDUCED PARKINSONISM

Mr LM who is on chlorpromazine therapy for schizophrenia developed parkinsonism. He was prescribed L-dopa 250 mg 4 times a day. He was not relieved, so the dose of L-dopa

was increased to 750 mg 4 times a day. This did not benefit him but further worsened the condition.

Qa. What could be the reason? Will you suggest any other drug for the control of parkinsonism?

Antipsychotic drugs such as chlorpromazine can induce parkinsonism due to antagonistic action at D_2-receptors in the nigrostriatal tract as they have high binding affinity for D_2-receptors. Levodopa, a precursor of dopamine is not useful in the setting described above as dopamine action is blocked in presence of antipsychotic drugs such as chlorpromazine. These agents may cause exacerbation of schizophrenia by increasing the dopamine levels.

Anticholinergic drugs such as trihexyphenydyl, benztropine and benzhexol restore the balance between dopaminergic and cholinergic activities.

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Chapter

14

Antiepileptics

CASE 1: CASE OF 'FOCAL AWARE TONIC' TYPE SEIZURE

A 26-year-old female RY, experienced an episode of seizure which was described by her husband. Husband informed, that her right thumb began suddenly to retract, followed by right hand movements. Within 1 min, her right arm and the right side of her face also began to contract. She recovered in 2 minutes. Following the event there was weakness in her right arm for about 6 hours. She was aware of the event and remembers the time during which the seizure occurred. MRI scan shows presence of neoplasm.

The seizure type is classified as 'focal aware motor' or 'focal aware tonic' type of seizure.

Qa. How do you define 'seizure' and 'epilepsy'?

A *seizure* is the "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain".

Epilepsy is defined as:

- At least 2 unprovoked seizures occurring more than 24 hours apart;
- One unprovoked seizure with increased risk for seizures (e.g. abnormal EEG or brain imaging);
- Diagnosis of epilepsy syndrome.

Qb. How do you classify seizures in epilepsy?

Seizure Classification is Based on 3 Key Features

1. **Where seizures begin in the brain:** Type of *seizure onset* affects choice of seizure medication.
    - Focal seizures start in an area or network of cells on one side of the brain
    - Generalized seizures occur when both sides of the brain or the whole hemisphere is involved at the onset.
    - Unknown onset if the onset of the seizure is not known.
    - Focal to bilateral seizure is a seizure that starts in one side or part of the brain and spreads to both sides and is called secondary generalized seizure.

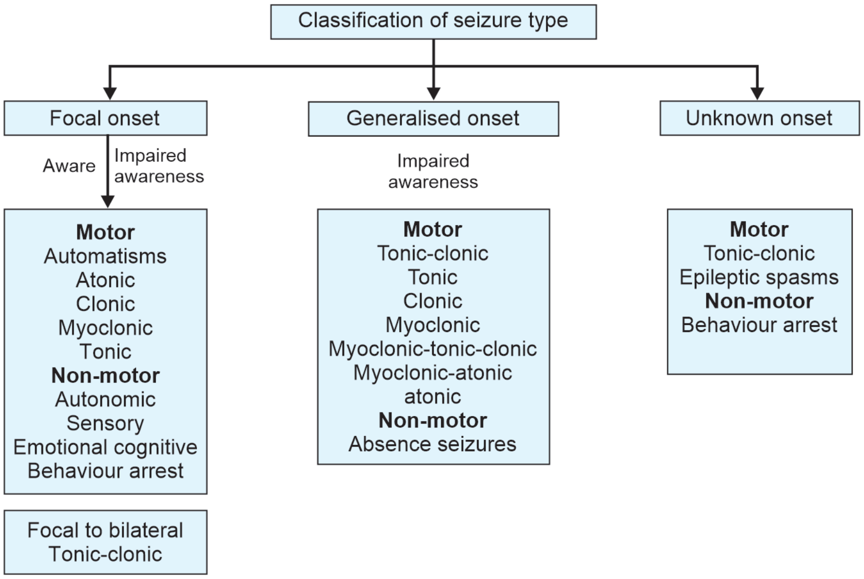
Classification of seizure type
Focal onset
Generalised onset
Unknown onset
Aware
Impaired awareness
Impaired awareness
Motor
Automatisms
Atonic
Clonic
Myoclonic
Tonic
Non-motor
Autonomic
Sensory
Emotional cognitive
Behaviour arrest
Focal to bilateral Tonic-clonic
Motor
Tonic-clonic
Tonic
Clonic
Myoclonic
Myoclonic-tonic-clonic
Myoclonic-atonic
atonic
Non-motor
Absence seizures
Motor
Tonic-clonic
Epileptic spasms
Non-motor
Behaviour arrest

Fig. 14.1: ILAE 2017 classification of seizure types

2. **Level of awareness during a seizure** is used to describe focal seizures, whereas in generalized sezures, it is presumed to affect a person's awareness or consciousness, thus *awareness is not used* in the description of generalized seizure.
    - *Focal aware:* If awareness remains intact, even if the person is unable to talk or respond during a seizure, the seizure would be called a focal aware.
    - *Focal impaired awareness:* If awareness is impaired or affected at any time during a seizure, would be called focal impaired awareness.
    - *Awareness unknown:* Sometimes, it is not possible to know if a person is aware or not.
3. **Motor or non-motor symptoms:** Focal and generalized seizures can be subclassified into motor and non-motor symptoms.
    - *Focal motor seizure:* This means that some type of movement occurs during the event. For example twitching, jerking, or stiffening movements of a body part or automatisms (automatic movements such as licking lips, rubbing hands, walking or running).
    - *Focal non-motor:* This type of seizure has other symptoms that occur first, such as changes in sensation, emotions, thinking or experiences.
    - *Generalized motor seizure* or generalized tonic clonic (GTC) seizure: Seizures with stiffening (tonic) and jerking (clonic) movements.
    - *Generalized non-motor seizure* includes absence seizures.

Qc. What is the clinical significance of classifying the 'seizure type' in epilepsy?

It is necessary to determine the type of seizure for the following reasons:

- To focus the diagnostic approach on a particular etiologic factor
- To select the appropriate drug therapy
- To conduct scientific investigations that require delineation of clinical and EEG phenotypes
- To provide vital information regarding the prognosis

Qd. Mention the therapeutic goal in the management of seizures in epilepsy.

The *therapeutic goal* is maximizing seizure control while minimizing adverse drug effects.

Qe. Enlist the various antiseizure medications (ASMs) for the management of epilepsy.

Antiseizure medications (ASM) include the following:

1st generation ASMs: Phenobarbital, mephobarbital, phenytoin, acetazolamide, corticosteroids/ACTH, primidone, ethosuximide.

2nd generation ASMs: Chlordiazepoxide, diazepam, carbamazepine, valproate, clonazepam, clobazam.

3rd generation ASMs: Vigabatrin, zonisamide, lamotrigine, oxcarbamazepine, gabapentin, topiramate, tiagabine, levetiracetam, pregabalin, rufinamide, lacosamide, eslicarbazepine acetate.

Qf. What are the mechanisms involved in the generation of focal seizure due to neoplasm, in a region of the brain, as in the case of RY?

Focal seizures occur when nerve cells in a part of the brain are involved, leading to the generation sudden, excessive, uncontrolled electrical signals. This results from depolarization within a group of neurons associated with increased activation of Na^+ channels and the Na^+ channels spend more time in the open state. There is *loss of refractory period induced by* Na^+ *channel inactivation and* K^+*-mediated hyperpolarization*.

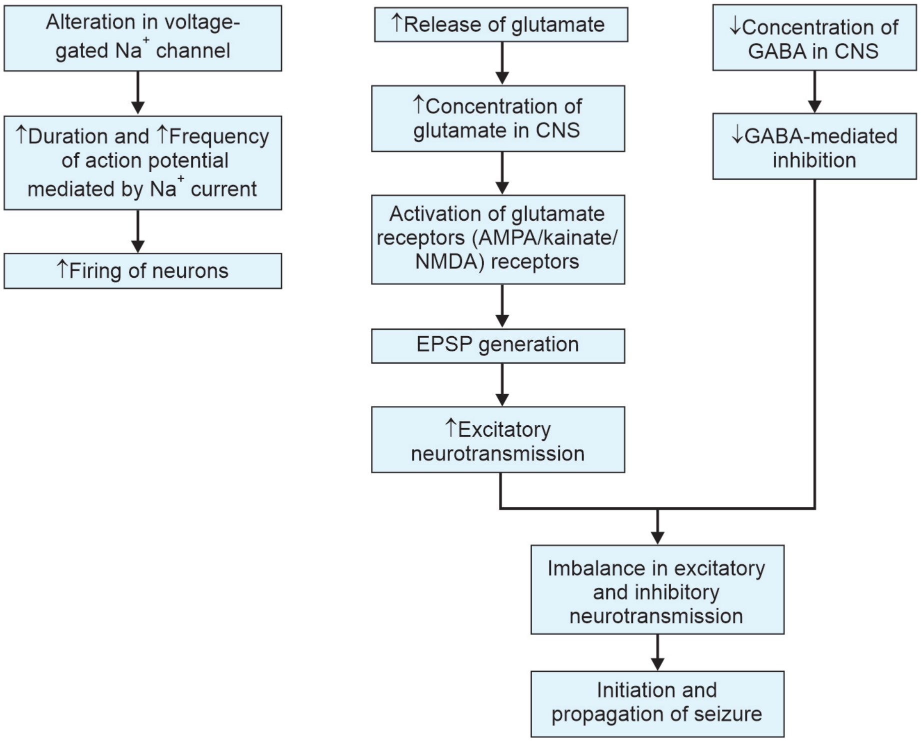
Alteration in voltage-gated Na+ channel
↑Duration and ↑Frequency of action potential mediated by Na+ current
↑Firing of neurons
↑Release of glutamate
↑Concentration of glutamate in CNS
Activation of glutamate receptors (AMPA/kainate/NMDA) receptors
EPSP generation
↑Excitatory neurotransmission
↓Concentration of GABA in CNS
↓GABA-mediated inhibition
Imbalance in excitatory and inhibitory neurotransmission
Initiation and propagation of seizure

Fig. 14.2: Pathophysiology of epilepsy

Imbalance between excitatory and inhibitory neurotransmission also contributes to the generation of seizures. Enhanced excitatory neurotransmission due to excess glutamate release and increased activity of glutamate receptor (NMDA, AMPA or Kainate receptor), and reduced GABAergic neurotransmission increases the frequency of generation of seizures.

Loss of surround inhibition mediated by GABAergic neurons causes synchronization with the adjacent neurons and propagation of action potentials to one side of the hemisphere and in turn involves one side of the body as in case of RY, where right side of the face and right arm was affected.

Qg. Which antiseizure medications (ASMs) would be useful for the management of focal seizures as in case of RY?

Most antiseizure medications (ASMs) with the exception of ethosuximide are appropriate for the management of focal seizures. Among the older antiepileptic medications **carbamazepine and phenytoin** are preferred for treatment. Newer antiepileptics such as **lamotrigine and topiramate** are equivalent to monotherapy with carbamazepine or phenytoin and are approved for the treatment of newly diagnosed or refractory focal seizures. **Levetiracetam, brivaracetam**, an analogue of levetiracetam, **tiagabine, zonisamide, gabapentin, pregabalin, lacosamide** can be used as *adjunctive* therapy for focal onset seizures.

Qh. Mention the mechanisms through which the antiseizure medications (ASMs) act in the treatment of focal seizures as in the case of RY.

Drugs	*Mechanism of action*
Phenytoin Fosphenytoin Carbamazepine Oxcarbamazepine Lamotrigine Zonisamide Lacosamide	• Delay the recovery of the inactivated sodium channels • Inhibit sustained repetitive firing of neurons
Phenobarbitone	• $GABA_A$ facilitatory action, *increases the duration of Cl^- ion influx* causing neuronal hyperpolarization and enhance inhibitory neurotransmission
Benzodiazepines (diazepam, lorazepam and clonazepam)	• Facilitate GABA action by i*ncreasing the frequency of opening of chloride channel* causing neuronal hyperpolarization and enhance inhibitory neurotransmission
Sodium valproate	• Inhibits sodium channel-mediated activation • Stimulates glutamic acid decarboxylase (GAD) and increases synthesis of GABA • Inhibits GABA transaminase (GABA-T), succinic aldehyde dehydrogenase (SAD) which are GABA degradative enzymes and thereby increase the levels of GABA with enhanced action of GABA • Inhibits T type calcium current
Gabapentin	• Binds to α2-delta-subunit of the calcium channel and promotes non-vesicular release of GABA
Levetiracetam	• Binds to synaptic vesicle protein SV2A in the brain and promotes vesicular release of GABA
Tiagabine	• Inhibits GABA transporter-1 and inhibits reuptake of GABA by presynaptic terminals
Vigabatrin	• Irreversible inhibitor of GABA transaminase (GABA-T), an enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This results in an increased concentration of GABA
Topiramate	• Blocks voltage-dependent sodium and calcium channels • Inhibits the excitatory glutamate pathway • Enhances the inhibitory effect of GABA
Pregabalin	• Binds with high affinity to the alpha 2-delta site (an auxiliary subunit of voltage-gated calcium channels) in CNS tissues

CASE 2: CASE OF 'FOCAL, IMPAIRED AWARENESS' TYPE OF SEIZURE

A 24-year-old female SK, attended the clinic with history of seizure disorder. She revealed that there was a sense of pain in the abdomen at the beginning of the seizure. Her brother noticed that during the event SK stares blankly and this is followed by chewing and swallowing movements. During the episode there is loss of awareness from the surroundings and SK does not respond to verbal or non-verbal stimuli. The attack lasted for 2 minutes.

EEG showed left temporal epileptic activity.

This would be classified as 'focal, impaired awareness' type of seizure.

Qa. Based on the clinical history and investigation findings, what is the probable diagnosis of the patient SK?

This is a case of complex partial seizures with involvement of temporal lobe. The seizure is preceded by an *aura* which is abdominal. There is *impairment of consciousness* and the seizure is accompanied with *automatisms* such as chewing and swallowing movements.

Case Continued

SK was initiated treatment with tab. phenytoin 5 mg/kg/day. SK was advised to maintain oral hygiene while on phenytoin therapy.

Qa. Why did the physician explain the importance of maintaining oral hygiene to SK, while on treatment with phenytoin? Explain with reasons.

Gum hyperplasia is commonly associated with phenytoin therapy and the occurrence and severity of hyperplasia of gums are related to the dose, serum concentration of phenytoin and duration of exposure to phenytoin. Enlargement of gums is due to proliferation of gum tissue resulting from the direct action of phenytoin on the gingival fibroblasts. Formation of dental plaque and food particles can cause irritation and increases the severity of gingival hyperplasia and halitosis may result. Therefore, educating the patient early on the importance of oral hygiene at the beginning of phenytoin therapy is useful in reducing the incidence and severity of gingival hyperplasia associated with phenytoin use.

Qb. Considering that SK is a 24-year-old young female treated with phenytoin, do you expect any changes in bone mineral metabolism with long-term phenytoin treatment?

Phenytoin therapy increases the risk of osteoporotic fractures. It is an inducer of hepatic cytochrome P450 isoenzymes which may cause vitamin D deficiency due to increased catabolism of vitamin D and undercarboxylation of the bone protein osteocalcin. Other mechanisms may include direct effect of phenytoin on bone cells, resistance to parathyroid hormone, inhibition of calcitonin secretion and impaired calcium absorption. Chronic phenytoin therapy thus results in a decrease in bone mineral density and increases the risk of bone fractures.

Qc. If there is coexisting depression with epilepsy, and the patient is on tricyclic antidepressant (TCA) medication, how would you expect the older antiepileptic drugs such as phenytoin, carbamazepine or phenobarbital to affect the concentration of tricyclic antidepressant drug when used concomitantly?

Studies have shown that patients with epilepsy commonly have coexisting depression disorders. Tricyclic antidepressants (TCAs) are substrates of hepatic cytochrome P450 enzymes. Older antiseizure medications (phenytoin, carbamazepine and phenobarbital) are susceptible to cause induction of hepatic enzymes. This results in increased metabolism of

TCAs and decrease in the serum concentration of the drug leading to therapeutic failure and increase in depression episodes.

Qd. How would you expect valproate to influence the serum concentration of tricyclic antidepressant when administered together?

Valproic acid causes inhibition of hepatic enzyme systems thereby increasing the serum concentrations of TCAs consequently increasing the risk of toxicity.

Qe. What changes in treatment can be considered by the physician to manage the risk of toxicity arising out of drug interaction?

The dose of antidepressant drug may be adjusted according to the stimulatory or inhibitory effects of the antiepileptic drug or a change in antiseizure medication should be considered.

Case Continued

Given that, SK is a 24-year-old young female in her child-bearing age, suffering from focal seizures.

Qa. If SK is on combined oral contraceptives, how would the antiepileptic drugs affect the efficacy of oral contraceptives? Explain.

Phenobarbital, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, perampanel, and felbamate have been shown to *increase the metabolism of ethinylestradiol content* of oral contraceptives thus reducing the therapeutic efficacy of oral contraceptives causing breakthrough bleeding and pregnancy. Patients receiving treatment with these drugs should be informed about the chances of contraceptive failure. A second contraceptive method (e.g. condoms, intrauterine devices, or spermicide) is recommended to avoid contraceptive failure.

Valproate, lamotrigine, gabapentin, tiagabine, zonisamide, levetiracetam, lacosamide, or pregabalin have minimal effect on the metabolism of oral contraceptives and their efficacy.

Qb. If SK wishes to conceive, which antiepileptic drugs should be used with caution in pregnancy? Are there any safer alternative antiepileptic drugs that can be used in pregnancy?

The antiepileptic drugs such as phenytoin, carbamazepine, phenobarbital, valproic acid, and topiramate have a teratogenic risk that needs to be considered during treatment.

Of the new antiseizure medications, lamotrigine and topiramate have known safety in pregnancy and are widely used. Folic acid 5 mg/d should be started before conception.

Case Continued

Despite SK receiving treatment with phenytoin, she continued to experience 2 to 3 seizures weekly and there was no improvement in seizure control. So the physician increased the dose of phenytoin to 10 mg/kg/day. Three days later, he presented to the clinic with complaints of unsteady gait and dizziness. The speech was slow and not clear. Examination of the eye showed nystagmus.

Qa. What do the clinical features described in case of SK suggest? Explain.

This could be a case of neurotoxicity resulting from high doses of phenytoin and is associated with various vestibular and cerebellar side effects like motor ataxia, muscle spasms, psychosis and visual disturbances. Long-term use of phenytoin at therapeutic and toxic levels, can lead to cerebellar atrophy. Phenytoin is susceptible to cause adverse effects because it has a narrow therapeutic window of 10–20 mg/L and wide pharmacokinetic variability.

Qb. Could these adverse effects have been avoided? If yes, how?

The adverse effects of phenytoin can be minimized by taking the following precautions:

- Choosing the most appropriate drug based on the clinical condition of the individual.
- Accurate dosing of drug particularly for drugs having narrow therapeutic index.
- Regular follow-up of patients for adverse effects, checking compliance and monitoring of plasma drug concentration.

Case Continued

The dose of phenytoin was gradually tapered followed by termination of phenytoin therapy and substituted with oral carbamazepine. The clinical condition of SK gradually improved.

Qa. What are the advantages of carbamazepine over phenytoin in the management of epileptic seizures in case of SK?

Carbamazepine has a number of advantages over phenytoin which are as follows:

1. Carbamazepine has less propensity to cause adverse effects on cognitive function. Phenytoin is known to cause cognitive impairment.
2. Carbamazepine has more favourable pharmacokinetic profile while phenytoin is a narrow therapeutic index agent with non-linear pharmacokinetics that is extensively bound to plasma proteins. Hence, carbamazepine has a better safety profile compared to phenytoin and dose adjustments with carbamazepine is easier.
3. Lack of cosmetic side effects with carbamazepine makes it more accepatable for a young female. Phenytoin is associated with dysmorphic effects, such as hirsutism, acne, gingival hyperplasia, and coarsening of facial features.

CASE 3: CASE OF ‘FOCAL TO BILATERAL TONIC-CLONIC’ SEIZURE

A 15-year-old girl KL, attends the clinic with history of 3–4 convulsions in the last few months. She complains of anxiety, irritability, difficulty in concentrating and abnormal smell occurring at the beginning of the seizure. She then loses consciousness followed by stiffening of all limbs followed by rhythmic jerking of all limbs. This lasts for 2 to 3 minutes after which she regains consciousness and is confused and exhausted for a variable period of time.

The seizure is classified as ‘focal to bilateral tonic-clonic’ seizure.

Qa. What is the basis of classifying the seizure as ‘focal to bilateral tonic-clonic’ seizure?

Seizure which originates in a focus of the cerebral hemisphere, spreads to the adjacent regions of the brain, propagating to the opposite cerebral hemispheres involving the whole of the brain and is thus classified as ‘bilateral tonic-clonic seizures’.

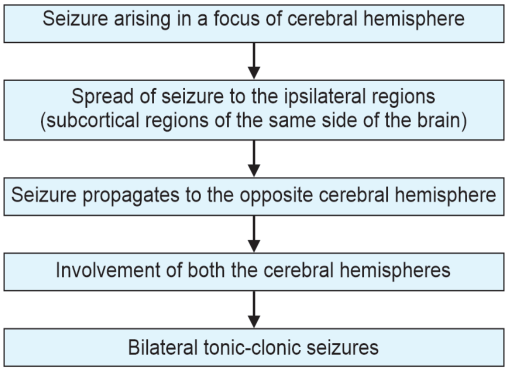
Seizure arising in a focus of cerebral hemisphere
Spread of seizure to the ipsilateral regions (subcortical regions of the same side of the brain)
Seizure propagates to the opposite cerebral hemisphere
Involvement of both the cerebral hemispheres
Bilateral tonic-clonic seizures

Fig. 14.3: Conversion of focal to bilateral tonic-clonic seizures

Qb. The physician decides to initiate therapy with carbamazepine for her epileptic seizures. Prior to initiation of carbamazepine, he ordered KL to carry out certain tests such as liver function test, blood cell counts. How are these investigations useful in the management of epilepsy with carbamazepine?

Carbamazepine has been associated with *hematologic and hepatic toxicities*. These reactions are believed to be unrelated to drug dosage and thus idiosyncratic. Aplastic anaemia and agranulocytosis have been reported with carbamazepine. However, severe hematologic toxicity is rare. Leukopenia is relatively common in patients taking carbamazepine. It is usually mild and often reverses despite continued administration of the drug.

Carbamazepine-related liver damage is rare but severe hepatic reactions have occurred. Carbamazepine hepatotoxicity is usually rapidly reversible with stopping therapy. In cases of severe injury progression to acute liver failure and death can occur.

Baseline (pretreatment) determination of KL's hepatic and hematologic status through laboratory tests, accompanied by follow-up testing would be useful in early detection of side effects and timely management.

CASE 4: CASE OF 'GENERALIZED TONIC-CLONIC' SEIZURE

A 32-year-old female AV, has seizures beginning with loss of consciousness followed by stiffening of all limbs and then rhythmic jerking of all limbs. She reveals that her grandfather had an epileptic disorder.

The epilepsy was diagnosed as 'generalized tonic-clonic' seizure and therapy was initiated with sodium valproate 125 mg twice daily.

Six months later, she reported that her seizures are relatively well-controlled but she has put on weight about 5 kgs.

Qa. She is keen to know whether the weight gain could be due to valproate use, and if the weight gain is due to valproate, she wishes to change her treatment.

She was informed that sodium valproate is known to cause stimulation of appetite with weight gain upon chronic treatment. The other gastrointestinal side effects are anorexia, nausea and vomiting.

She was explained that **valproic acid** has been the antiepileptic drug of choice for patients with generalised tonic clonic seizures and multiple seizure types including myoclonic seizures. The newer medications **(lamotrigine, topiramate, zonisamide, levetiracetam)** are equally effective and have better side effect profiles, and thus can be considered for treatment.

If she wishes to change her treatment, sodium valproate should be gradually tapered and *levetiracetam* may be introduced.

Qb. What are the other side effects expected with valproate use in epilepsy? How should a patient be monitored on valproate therapy?

Valproate-related side effects include *gastrointestinal side effects* such as anorexia, nausea, vomiting and weight gain. *Central nervous system* side effects such as sedation, ataxia and tremor can occur. *Elevation of hepatic transaminases* in plasma in the initial months of therapy may be seen. However, fulminant hepatitis is a rare complication but fatal. Cases of *acute pancreatitis* has been reported with valproate use. It can cause direct *bone marrow suppression* leading to aplastic anaemia or peripheral cytopenia. Rash and alopecia can also occur. *Teratogenic side effects* such as neural tube defects in the foetus is possible.

Liver function test, amylase and/or lipase, and complete blood cell count (CBC) results should be monitored during drug treatment.

Qc. The generalized seizure involves a tonic phase (stiffening), clonic phase (shaking) followed by postictal phase. Explain the molecular mechanism responsible for the clinical presentation seen in case of AV.

There is sudden and rapid generation of electrical discharges in an area of the brain. The loss of surround inhibition mediated by GABA results in hyperexcitatory state due to glutamate and facilitates the propagation of nerve impulses. The sustained and repetitive firing of neurons cause stiffening of agonist and antagonist group of muscles, referred to as **tonic phase**.

Clonic phase is characterized by gradual recovery of inhibitory GABA activity with existing glutamate (AMPA and NMDA receptor) mediated excitation. So, the oscillation between excitatory and inhibitory component manifests clinically as jerking movements.

The **postictal phase** is characterized by enhanced GABA-mediated inhibition which causes symptoms of confusion.

CASE 5: DRUG THERAPY OF 'ABSENCE SEIZURES'

A 9-year-old boy LM, has recurrent episodes of loss of conscious activity with a blank look that lasts for few seconds. There is upward deviation of eyes and fluttering of eyelids. His friends have noticed sudden pause in the middle of a sentence while talking. He is not aware of what has happened during the episode and looks confused. There is no major motor manifestation during the episodes.

There are complaints from his school of not taking down the instructions from the teachers and submitting incomplete work. The patient's neurologic examination is totally normal.

The seizure type is classified as 'typical absence seizure'.

Qa. Explain the mechanisms at the molecular level that result in clinical presentation described in the case of LM.

The thalamus has a central role in the generation of absence seizure. It is the relay station for information transfer in the brain. There exists a loop comprising of glutamatergic corticothalamic neurons and thalamocortical relay neurons.

These cortex—thalamus connecting neurons additionally innervate *GABAergic neurons in the reticular thalamic nucleus generating the hyperpolarization* resulting in activation of T type calcium channels.

During absence seizure, *activation of highly expressed T type calcium channel mediated by hyperpolarsation* results in burst firing. Burst firing generates *synchronization of neural network* and recruits additional neurons to the burst firing state resulting in spreading and propagating the oscillations. This large depolarization in the cortex registers as spike and wave pattern on the EEG.

In the awake state, there is loss of awareness from surroundings, which is manifested as 'blank stare' and this may happen for a brief duration usually less than 30 seconds for several times in a day.

Qb. Which are the drugs used for the treatment of absence seizures?

Antiepileptic drugs approved for the treatment of absence seizures are **ethosuximide and valproic acid. Ethosuximide** is the first-line choice for the treatment of absence seizures because of better tolerability profile compared to valproate. **Valproate** is preferred if the patient with absence seizures does not respond to ethosuximide or if tonic-clonic seizures are present or emerge during therapy.

Available evidence suggests that **lamotrigine** is also effective for newly diagnosed absence epilepsy but is not approved by FDA for this indication.

Clonazepam is unique among BZD because it acts specifically at $GABA_A$ receptors of the reticular thalamic nucleus, thus decreasing the activation of inhibitory thalamic reticular neurons. This action suppresses GABA-mediated hyperpolarization of the thalamic relay neurons and the burst activity of the Ca^{2+} channel which is the cause of absence seizures. Therapy with clonazepam is limited by prominent CNS side effects (sedation, ataxia, and mood changes) and development of tolerance to its antiepileptic effect after long-term use.

CASE 6: DRUG THERAPY IN 'PARTIAL SEIZURES'

A 75-year-old man VK, had 2 episodes of partial seizures. He was admitted to the hospital for further evaluation and treatment.

Past medical history was remarkable for history of stroke one year ago, asthma, type 2 diabetes mellitus, gastroesophageal disease, hypercholesterolaemia, hypertension and osteoporosis.

Medications included aspirin, atorvastatin, an inhaler, ranitidine, telmisartan, metformin and glimepiride.

The patient was treated with levetiracetam and had no further seizures. VK was discharged with a prescription for levetiracetam 750 mg twice a day. EEG was normal.

Qa. Given that, VK is a 75-year-old man with comorbid conditions and on multiple medications. Which antiepileptic drugs are preferred—older or newer?

The most common older drugs are valproic acid, phenytoin, carbamazepine, primidone and phenobarbital. The newer drugs are gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, zonisamide, oxcarbamazepine and pregabalin. Felbamate is rarely used because of potential for serious side effects.

Newer antiepileptic drugs have a better tolerability profile than older drugs. They have a lower risk for drug interactions due to lack of cytochrome P450-dependent metabolism. The patients are less likely to discontinue drugs leading to greater adherence to treatment. Older drugs induce hepatic enzymes, consequently leading to increased metabolism of hormones such as oestrogen and testosterone, vitamins such as vitamin D and K as well as medications that are prescribed for the other conditions. This may have consequences including alteration in sexual function and increased likelihood of thinning of the bones (osteoporosis). Drugs given for high blood pressure, high cholesterol may also be affected.

Unlike the new antiepileptic drugs, the older drugs are more likely to be associated with organ toxicities and thus the need for monitoring of liver functions, blood counts and other blood tests. Serum level monitoring of antiepileptic drugs which have a narrow therapeutic window should be considered.

Pharmacokinetic variability of newer antiseizure medications is less pronounced and more predictable under various physiologic conditions.

CASE 7: DRUG THERAPY OF 'STATUS EPILEPTICUS'

A 55-year-old male PQ, known epileptic on irregular treatment was presented to an emergency department with a history of generalized-tonic-clonic seizures. In the

emergency department, the patient had a few episodes of seizures without recovery of consciousness in between the attacks.

Qa. Identify the emergency situation described above as in case of PQ.

A seizure that lasts longer than 5 minutes, or having more than 1 seizure within a 5 minutes period, without returning to a normal level of consciousness between episodes is called **status epilepticus**. The clinical presentation of PQ is suggestive of status epilepticus.

Qb. Comment on the importance of IV route in the management of status epilepticus. Which antiepileptic drugs are available for IV therapy in the management of this situation?

The therapeutic goal is to rapidly terminate seizure activity because status epilepticus becomes more resistant to treatment, the longer the seizure continues. Intravenous administration of rapidly acting anticonvulsant should be started in this situation so that the therapeutic drug concentration in the plasma is achieved rapidly and is available for action on the target site.

Lorazepam, phenytoin, fosphenytoin and phenobarbital are the agents most commonly used as IV therapy in the treatment of status epilepticus. IV form of levetiracetam, lacosamide, valproate are available which can be used for SE but experience is limited with the use of these drugs.

Qc. How is fosphenytoin superior to phenytoin for IV therapy in the management of epilepsy?

Fosphenytoin is a prodrug of phenytoin and highly water soluble. This makes it suitable for IM and IV use without the need for propylene glycol. Phenytoin is water insoluble and requires polypropylene glycol for solubilisation in an alkaline solution raising the pH of the formulation.

Fosphenytoin has a lower potential for local tissue and cardiac toxicity compared to phenytoin due to the absence of polypropylene glycol in the formulation.

Fosphenytoin can be infused at a faster rate due to its better tolerability profile while phenytoin should not be infused at a rate greater than 50 µg/min to minimize the risk of hypotension and acute cardiac arrhythmias.

Qd. In a situation where IV access is not feasible, can phenytoin be administered intramuscularly? Explain with reasons.

Phenytoin is not recommended for intramuscular (IM) use. The parenteral formulation of phenytoin is highly alkaline and precipitates into crystals in the muscle after being injected due to sudden change in pH. This in turn impairs absorption of the drug from the injection site and causes tissue necrosis and discomfort at the injection site. The formulation is best suited for IV use.

Case Continued

PQ was initiated treatment with lorazepam 0.1 mg/kg given intravenously at 2 mg/minute. This was followed by the administration of an initial loading dose of phenytoin 20 mg/kg. Another dose of phenytoin 10 mg/kg was given when there was failure to terminate seizures.

Qa. Why is lorazepam selected as the first-line antiepileptic drug for the management of status epilepticus?

Lorazepam is preferred over phenytoin as the first-line agent in the management of status epilepticus because of the limitations of phenytoin on infusion rates resulting in delayed onset of peak effect of the drug. Lorazepam administered intravenously, quickly reaches the therapeutic plasma concentration and produces immediate therapeutic effect.

Lorazepam is better suited than diazepam in status epilepticus because of *lesser local thrombophlebitic complications* and *more sustained action* than that of diazepam. Diazepam is highly lipid soluble and so has good penetration into the brain with a very rapid onset of action when given intravenously. However, because of its lipid solubility, it is rapidly redistributed to the peripheral tissues resulting in shorter duration of action. Lorazepam has a longer duration of action than diazepam because it is less lipid soluble and consequently does not undergo the rapid redistribution into peripheral tissues seen with diazepam.

Qb. Despite treatment of PQ with lorazepam and phenytoin the seizures do not subside. What is the next line of treatment?

Status epilepticus that does not respond to lorazepam and a longer-acting agent, e.g. phenytoin/fosphenytoin is considered *refractory status epilepticus*. Phenobarbital may be useful for treatment of SE. The most commonly used anaesthetic agents for refractory status epilepticus are midazolam and propofol.

Qc. Phenobarbital is less commonly used than carbamazepine, phenytoin or valproate for long-term treatment of epilepsy. Why?

a. The major drawback of phenobarbitone as an antiepileptic is its **sedative action**.
b. Long-term administration (as needed in epilepsy) may produce additional side effects like **behavioural abnormalities, impairment of learning and memory, hyperactivity in children, mental confusion in older people.**
c. Rashes, megaloblastic anaemia and osteomalacia occur in some patients with prolonged use.

It has become less popular than carbamazepine, phenytoin or valproate because of its dulling and behavioural side effects.

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Chapter

15

Antidepressant Drugs

CASE 1: CASE OF MAJOR DEPRESSION

A 55-year-old male patient 'XY', presents to the psychiatrist with complaints of depressed mood.

He mentions that he is facing depression identical to what he has experienced previously.

He was diagnosed with major depression for the first time 20 years ago and was treated with imipramine up to 150 mg/day, with good results.

The second depression episode occurred 15 years ago, which was treated with imipramine. But the symptoms remitted after 4 to 6 weeks.

He denies illicit drug use or any recent traumatic events.

The man states that although he is sure he is experiencing another major depression, he would like to avoid imipramine this time because it produced unacceptable side effects such as dry mouth, dry eyes and constipation.

Q1a. What is the pathophysiology of depression? How do the antidepressants play a role in alleviating depression?

The hypothesis proposed to explain the pathophysiology of depression is as explained below:

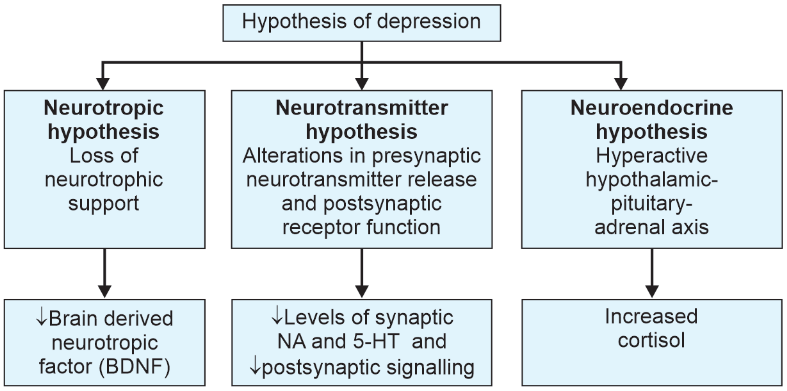

Hypothesis of depression
Neurotropic hypothesis
Loss of neurotrophic support
Neurotransmitter hypothesis
Alterations in presynaptic neurotransmitter release and postsynaptic receptor function
Neuroendocrine hypothesis
Hyperactive hypothalamic-pituitary-adrenal axis
↓Brain derived neurotropic factor (BDNF)
↓Levels of synaptic NA and 5-HT and ↓postsynaptic signalling
Increased cortisol

Fig. 15.1: Hypothesis of depression

Neurotrophic hypothesis: Proposes that depression results from decreased neurotrophic support, leading to neuronal atrophy, decreased hippocampal neurogenesis and loss of glia. BDNF levels in CSF and serum, decline with chronic stress and pain, resulting in hippocampal atrophy (5–10% loss of volume of hippocampus). BDNF is critical in the regulation of neuronal plasticity, resilience and neurogenesis. Antidepressant treatment blocks or reverses this neurotrophic factor deficit and thereby reverses the atrophy and cell loss.

Neurotransmitter hypothesis: Monoamines are neurotransmitters that include serotonin, dopamine, norepinephrine and epinephrine.

The therapeutic effect of antidepressants is due to sustained increase in the synaptic levels of the monoamine neurotransmitters, serotonin, norepinephrine and dopamine and increased efficiency of serotonergic and adrenergic neurotransmission.

Neuroendocrine hypothesis: Abnormal neurophysiology and central nervous system function may cause the depressed state and hypothalamic-pituitary-adrenal axis (HPA) overactivity. Corticotropin-releasing hormone (CRH) is released from the hypothalamus which induces the secretion of pituitary corticotropin stimulating the adrenal gland to release cortisol into the plasma.

Qb. How do you classify the currently available antidepressant agents based on their mechanism of action?

Drug class *(on the basis of mechanism of action)*	*Drugs*
Tricyclic antidepressants (TCAs): Block the reuptake of serotonin and norepinephrine in presynaptic terminals, which leads to increased concentration of these neurotransmitters in the synaptic cleft	**Tertiary amines:** Imipramine, clomipramine, amitryptyline, trimipramine, doxepin **Secondary amines:** Desipramine, nortriptyline, protriptyline
Selective serotonin reuptake inhibitors (SSRIs): Block the reuptake of serotonin into neurons	Escitalopram, fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline
Serotonin norepinephrine reuptake inhibitors (SNRIs): Block the reuptake of norepinephrine	Venlafaxine, desvenlaxine, duloxetine, milnacipran, tofenacin
Norepinephrine/dopamine-reuptake inhibitor (NDRI): Inhibition of the transporters involved in the uptake of the neurotransmitters norepinephrine and dopamine	Bupropion
Norepinephrine reuptake inhibitors (NRIs)	Reboxetine, viloxazine
Tetracyclic antidepressants (TeCAs)	Amoxapine, maprotilene
MAO inhibitors: Inhibition of breakdown of serotonin and norepinephrine in the brain	a. Non-selective: Phenelzine isocarboxazid, tranylcypromine b. Reversible inhibitors of MAO-A: Brofaromine, moclobemide, toloxatone

Serotonin receptor modulators	
Serotonin antagonist and reuptake inhibitors (SARIs): Antagonize receptors such as 5-HT2A and inhibit the reuptake of serotonin, norepinephrine, and/or dopamine.	Trazodone, nefazodone
Serotonin modulators and stimulators (SMSs): Selective inhibition of serotonin reuptake and enhancement of serotonergic activity	Vilazodone, vortioxetine
Noradrenergic and specific serotonergic antidepressants (NASSAs): Antagonize both noradrenaline α2-autoreceptors and noradrenaline α2-heteroreceptors, and certain serotonin receptors such as 5-HT2A and 5-HT2C	Mirtazapine

Qc. Why is there a delay in maximal efficacy with all antidepressants in the management of depression?

A. The pathophysiological basis of depression is reduced availability of the neurotransmitters, serotonin, norepinephrine or dopamine in the synapse resulting in low level of postreceptor signaling (Fig. 15.2A).

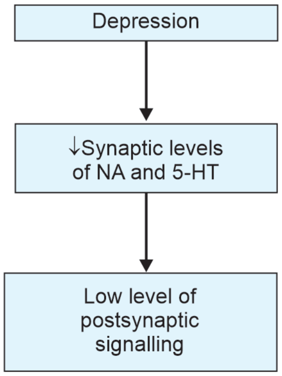
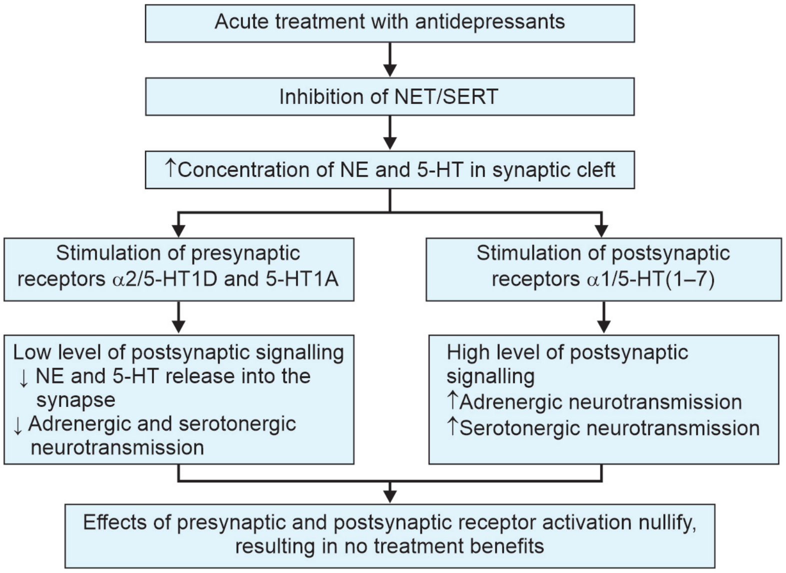

Depression
↓Synaptic levels of NA and 5-HT
Low level of postsynaptic signalling

Fig. 15.2A: Pre-treatment neurotransmitter response in depression

B. Initial treatment with antidepressants blocks norepinephrine or serotonin transporter (NERT/SERT) increasing the concentrations of NE and 5-HT in the synapse which in turn stimulates the postsynaptic α1/5-HT (1–7) receptors to enhance noradrenergic and serotonergic neurotransmission. However, this effect is offset by a negative feedback mechanism exerted by α2 and 5-HT1D/5-HT1A receptors to inhibit the release of NE and 5-HT and the concentration of NE and 5-HT returns to pre-treatment levels leading to lack of efficacy of antidepressant drug Fig. 15.2B.

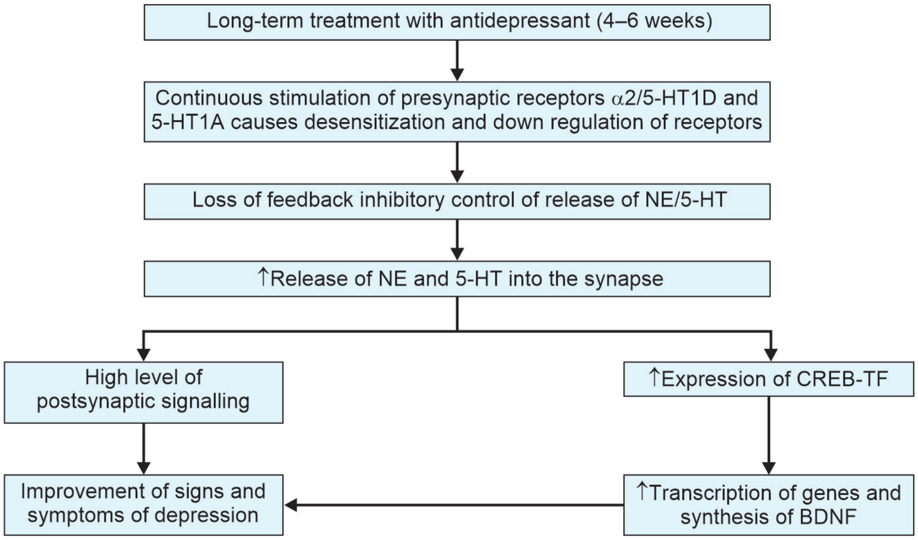

Acute treatment with antidepressants
Inhibition of NET/SERT
↑Concentration of NE and 5-HT in synaptic cleft
Stimulation of presynaptic receptors α2/5-HT1D and 5-HT1A
Stimulation of postsynaptic receptors α1/5-HT(1–7)
Low level of postsynaptic signalling
↓ NE and 5-HT release into the synapse
↓ Adrenergic and serotonergic neurotransmission
High level of postsynaptic signalling
↑Adrenergic neurotransmission
↑Serotonergic neurotransmission
Effects of presynaptic and postsynaptic receptor activation nullify, resulting in no treatment benefits

NET: Norepinephrine transporter; SERT: Serotonin transporter

Fig. 15.2B: Initial antidepressant treatment and resulting neurotransmitter response

C. Chronic treatment over a period of 4–6 weeks, causes desensitization and downregulation of presynaptic α2 and 5-HT1D/5HT1A (autoreceptors and heteroreceptors), associated with increased release of NE and 5-HT resulting in high level of postsynaptic signaling.

Also there is increased expression of CREB (cAMP response element binding protein) transcription factor which causes increased transcription of genes with subsequent increase in expression of brain-derived neurotropic factor (BDNF) that increases neurogenesis and synaptic connectivity in cortical areas such as hippocampus. Consequently, there is improvement in the signs and symptoms of depression Fig. 15.2C.


Long-term treatment with antidepressant (4–6 weeks)
Continuous stimulation of presynaptic receptors α2/5-HT1D and 5-HT1A causes desensitization and down regulation of receptors
Loss of feedback inhibitory control of release of NE/5-HT
↑Release of NE and 5-HT into the synapse
High level of postsynaptic signalling
↑Expression of CREB-TF
Improvement of signs and symptoms of depression
↑Transcription of genes and synthesis of BDNF

CREB: cAMP response element binding protein; BDNF: brain-derived neurotropic factor

Fig. 15.2C: Chronic antidepressant treatment and resulting neurotransmitter response

Qd. What are the mechanisms underlying side effects of imipramine? Identify the mechanism responsible for dry mouth, dry eyes and constipation experienced by the patient XY.

Imipramine, a tricyclic antidepressant (TCA), in addition to acting as a reuptake inhibitor of serotonin and norepinephrine also acts on muscarinic (cholinergic), histamine, adrenergic and dopamine receptors. The anticholinergic side effects are most predominant. Side effects such as dry mouth, dry eyes and constipation are anticholinergic in nature due to blockade of muscarinic receptors by imipramine and is manifested by the patient XY.

The *antihistaminergic effects* include sedation, weight gain and confusion. The *antiadrenergic effects* include orthostatic hypotension, reflex tachycardia, drowsiness and dizziness.

Imipramine (TCA) can also bind to *sodium channels* and exhibit cardiovascular side effects such as conduction delays.

Case Continued

The patient 'XY' was treated with fluoxetine 20 mg/day. In 2–3 weeks he started feeling better and the patient wellbeing improved.

Qa. How are selective serotonin reuptake inhibitor (SSRI) better than tricyclic antidepressant (TCA) in the treatment of depression?

Selective serotonin reuptake inhibitor (SSRI) unlike tricyclic antidepressant (TCA) are more *selective in their mechanism of action* with specific action on 5-HT transporters inhibiting the reuptake of serotonin and increases the efficiency of serotonergic neurotransmission producing a therapeutic effect.

SSRIs are also associated with *fewer adverse effects* than TCAs due to their on-target action. TCAs on the otherhand has off-target effects because of their binding affinity for a number receptors and channels with related side effects.

Qb. What are the common side effects the physician would expect with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) and mention the underlying mechanisms for the side effects?

Nausea, a common side effect of SSRI therapy can be a local effect but most likely results from stimulation of 5-HT3 receptors and can usually be alleviated by reducing the dose of the SSRI. SSRIs may also cause transient and bothersome increase in GI motility. *Diarrhoea* is limited to the first few weeks of therapy, and is due to high levels of serotonin in gastric and intestinal mucosal enterochromaffin cells, and stimulation of 5-HT3 receptors along the GI tract. Paroxetine, in contrast to fluoxetine can cause *constipation* due to mild antimuscarinic effect. SSRI-induced *sexual dysfunction* may be due to the stimulatory action of serotonin on 5HT2C receptors. *Sleep disturbances* are commonly reported with SSRIs.

Qc. What is the potential risk if fluoxetine is combined with imipramine?

Fluoxetine may cause a two-to-fourfold increase in plasma concentration of imipramine, and is possibly associated with signs of toxicity including decreased energy, psychomotor retardation, sedation, dry mouth and memory loss. The mechanism of this interaction may be attributed to the potent inhibitory effect of fluoxetine on the CYP-2D6 enzymes which metabolizes tricyclic antidepressants, thus, increasing the concentration of imipramine and imipramine-mediated side effects.

Case Continued

Two years later, XY was brought to the clinic with complaints of relapse of depressive symptoms. On questioning, the patient it was revealed that he experienced problems of orgasm and ejaculation, because of which he stopped taking fluoxetine. Subsequently, a few months later there was recurrence of depressive symptoms.

XY was recommended bupropion 150 mg daily and he was counselled that bupropion would treat depression and will be helpful in restoring sexual desire and relieving delayed orgasm.

Qa. How does bupropion act? Mention the side effects associated with bupropion use as an antidepressant.

Bupropion acts by inhibiting reuptake of dopamine and has negligible effects on serotonin.

Nausea, insomnia, agitation and jitteriness are the most common and are likely due to the stimulatory effect of dopamine. Seizures are a risk but are unlikely with therapeutic dosing of bupropion provided that patients are not predisposed. Bupropion may decrease appetite.

CASE 2: CASE OF SEROTONIN SYNDROME

A 55-year-old female patient 'RY' with history of chronic cancer pain has been on treatment with tramadol for pain and was prescribed fluoxetine 20 mg per day for depression 1 month ago. She was admitted to the emergency department for anxiety and agitation, including increased sweating of palms and restless legs. Her physical examination was significant for tachycardia, hypertension and agitation. Neurologic examination was positive for hyper-reflexia and clonus.

Serotonin toxicity was suspected and fluoxetine and tramadol were discontinued. Cyproheptadine 4 mg and diazepam 5 mg were administered to reduce agitation and serotonergic symptoms.

Qa. What is serotonin syndrome?

Serotonin toxicity (ST) or often referred to as serotonin syndrome, is a potentially lethal adverse effect due to serotonergic overactivity resulting from stimulation of both the peripheral and central postsynaptic 5-HT1A and, most notably 5-HT2A receptors.

It is precipitated via the therapeutic use of serotonergic drugs, an overdose of serotonergic drugs, or classically, as a result of a complex drug interaction between two serotonergic drugs that work by different mechanisms. A multitude of drug combinations can result in serotonin syndrome.

Qb. What are the manifestations of serotonin syndrome? How are the clinical signs and symptoms exhibited by the patient RY consistent with serotonin toxicity?

Serotonin syndrome represents a constellation of signs and symptoms which manifests in neuromuscular, gastrointestinal, autonomic and central nervous system.

Neuromuscular symptoms are characterized by hyper-reflexia, myoclonus and tremor. Gastrointestinal symptoms manifest as diarrhoea and constipation. Autonomic nervous system effects include diaphoresis, hypertension, tachycardia, hyperthermia, piloerection and muscular rigidity. There are also changes in mental status, confusion and restlessness.

The clinical signs and symptoms exhibited by the patient RY to the hospital represent manifestations of serotonin toxicity described above.

Qc. What are the mechanisms involved in serotonin toxicity?

Potential mechanisms responsible for serotonin toxicity include:

- Increased serotonin synthesis or release
- Reduced serotonin reuptake
- Direct serotonin receptor activation
- Inhibition of cytochrome P450 enzymes with reduced metabolism

Qd. Mention few specific agents that are likely to cause serotonin toxicity. Which drug combination used in case of RY could have led to serotonin toxicity?

Specific agents that may be implicated in serotonin toxicity include amphetamines and their derivatives, analgesics, antidepressants/mood stabilisers, monoamine oxidase inhibitors, SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antiemetics and antimigraine drugs.

RY is on treatment with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) which increases the concentration of serotonin in the synapse. Tramadol partly acts by inhibiting the reuptake of both norepinephrine and serotonin and increases serotonergic transmission. Therefore, coadministration of tramadol with fluoxetine may increase intrasynaptic levels of serotonin giving rise to serotonin toxicity.

Qe. What will be the line of treatment in this case? What precautions can be taken to avoid this adverse effect?

The patient ‘RY’ was instructed to stop taking fluoxetine and reduce his tramadol dose to his prescribed dose. Supportive treatment may be necessary and for more severe reactions, the serotonergic antagonist cyproheptadine is most commonly prescribed. Dantrolene has been administered successfully to manage hyperthermia.

Because of the widespread use of serotonergic drugs, clinicians must maintain a high clinical suspicion for serotonin syndrome. Early recognition and treatment of serotonin syndrome can prevent significant morbidity and mortality.

CASE 3: CASE OF CHEESE REACTION

A 37-year-old female LM, taking phenelzine for mood disorder, developed severe headache, palpitation one hour after taking cheese. The blood pressure readings were 180/100 mmHg.

Qa. Explain the reasons for these signs and symptoms exhibited by the patient LM.

An acute attack of hypertension can occur in a person taking oral monoamine oxidase inhibitor (MAOI) drug combined with cheese containing substantial amount of tyramine. Phenelzine is an irreversible monoamine oxidase inhibitor (MAOI). Inhibition of MAO inhibits degradation of norepinephrine and tyramine. Tyramine, an indirectly acting sympathomimetic, causes the release of catecholamines. This results in increased concentration of catecholamines in the synaptic cleft which leads to a dangerous rise in blood pressure and associated complications such as stroke and myocardial infarction.

The other tyramine containing food and drinks including aged cheese and meat, chicken liver, red wine, tap beer, pickled or smoked fish, fava beans are known to cause cheese effect.

Qb. Explain the rationale behind the use of selegiline, a selective MAO-B inhibitor in the treatment of depression.

Selegiline is an irreversible inhibitor of MAO enzymes. Orally administered selegiline, approved as an adjunctive treatment in Parkinson’s disease, is specific for MAO-B and generally devoid of clinically significant antidepressant activity, as well as the potential for a tyramine provoked event. However, ***at high oral dosages of selegiline***, the specificity for MAO-B is lost and ***non-selective inhibition of MAO*** confers antidepressant effects with the risk of a tyramine-provoked event.

At oral dosages between 30–60 mg/day (3–6 times greater than that used in the treatment of PD), selegiline is used for depression.

Qc. What is the advantage of delivery of selegiline via transdermal route in the treatment of depression?

The use of orally administered MAO inhibitor antidepressants is limited by the risk of tyramine-provoked events when combined with dietary tyramine.

Delivery of selegiline, transdermally bypasses hepatic first pass metabolism, thereby avoiding significant inhibition of gastrointestinal and hepatic MAO-A activity (i.e. reduced risk of tyramine-provoked events) while still providing sufficient levels of selegiline in the brain to produce an antidepressant effect.

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Chapter

16

Antipsychotic Drugs

CASE 1: DRUG THERAPY IN SCHIZOPHRENIA

A 27-year-old female 'AB', is brought to a psychiatric clinic by her relatives with complaints of the patient behaving abnormally for last 1 year. The patient 'AB' who used to be involved in social gatherings has suddenly lost interest in social interactions and prefers to remain indoors. She remains poorly dressed and takes no interest in cooking or doing household work. She remains preoccupied with herself and is inattentive. Family members have seen her mumbling and talking to herself in isolation. When asked she says she can hear voices speaking to her. She has a belief that people are conspiring against her and feels insecured. She also becomes agitated and reacts when she is told something. There is no history of smoking, alcohol or any other substance abuse or head injury or any medical illness.

You have diagnosed AB as a case of schizophrenia and is prescribed tab. olanzapine 10 mg per day.

Qa. Mention the manifestations from the clinical history which suggest schizophrenia in case of AB.

The history of the patient suggests that she is experiencing positive symptoms such as auditory hallucinations and delusion of persecution, negative symptoms like social withdrawal and cognitive deficits such as loss of memory and lack of concentration.

Qb. What is the neurological basis for the symptoms experienced by the patient?

The positive symptoms correlate with mesolimbic dopaminergic hyperactivity. Negative symptoms and cognitive deficits correlate with mesocortical dopaminergic hypoactivity.

Qc. What is the therapeutic goal of antipsychotic drugs in the treatment of schizophrenia?

The therapeutic goal of antipsychotic drugs in the treatment of schizophrenia is as follows:

1. Reduce dopaminergic hyperactivity in the mesolimbic system
2. Enhance dopaminergic hypoactivity in the mesocortical system

Qd. How do you classify the currently available antipsychotic agents?

I. Classical or Typical Neuroleptics

A. Phenothiazines

i. With aliphatic tertiary amine side chain

Chlorpromazine

ii. With piperidine moiety in side chain
Thioridazine
iii. With piperazine moiety in side chain
Trifluperazine, fluphenazine

B. Thioxanthenes

Flupenthixol, thiothixene

C. Butyrophenones

Haloperidol, droperidol

D. Miscellaneous

Pimozide, penfluridol, molindone, sulpiride

II. Novel or Atypical Neuroleptics

Clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, asenapine.

Qe. Explain the rationale behind prescribing olanzapine in patient AB, who is experiencing positive symptoms, negative symptoms and cognitive deficits.

Olanzapine, an atypical antipsychotic has predominant action on serotonergic receptors, 5-HT2A and 5-HT2C receptors, and less action on D2-receptors. The action at 5-HT2A receptors increase dopamine release in prefrontal cortex and thereby enhance dopaminergic neurotransmission which leads to improvement in negative symptoms and cognitive function.

It also blocks some dopamine receptors in the brain, correcting the overactivity of dopamine in the mesolimbic system and alleviate positive symptoms of schizophrenia. Olanzapine is therefore effective in the treatment of positive symptoms, negative symptoms and cognitive decline.

With regard to side effects, olanzapine is less likely to produce extrapyramidal side effects and hyperprolactinaemia than typical antipsychotics due to lesser action on mesolimbic system and nigrostriatal tract.

Thus, olanzapine, an atypical antipsychotic has greater efficacy than typical antipsychotics in the treatment of negative and cognitive symptoms of schizophrenia with reduced risk of extrapyramidal side effects.

Qf. The atypical antipsychotic drugs produce less neurological adverse effects than typical antipsychotics even though they block D2-receptors. Explain with reasons.

Although the atypical antipsychotics have D2-antagonistic action they are generally less likely to cause drug-induced parkinsonism and tardive dyskinesia than typical antipsychotics because at least 78% of D2-receptors must be blocked in the striatum to produce extrapyramidal side effects and 68% is required for predicted response. Atypical antipsycotics block less than 78% of the dopamine receptors, so they produce therapeutic action with less incidence of extrapyramidal side effects.

Qg. First generation antipsychotics differ in their potency. Explain how potency of the typical antipsychotics play a role in determining the drug's adverse effect profile with examples.

High potency antipsychotics such as haloperidol have strong binding affinity and more selective action on D2-receptors than on histaminic H1, α1-adrenergic and muscarinic receptors and therefore is more likely to cause extrapyramidal side effects. Conversely chlorpromazine, which is a low potency antipsychotic, acts as strong H1-blocker-inducing weight gain, α1-blocker-inducing orthostatic hypotension and blocker at muscarinic receptors causing anticholinergic side effects such as dry mouth, visual blurring and constipation.

Thus, extrapyramidal side effects are more common with potent typical antipsychotics and other side effects such as orthostatic hypotension, weight gain and anticholinergic side effects are common with less potent typical antipsychotics.

Qh. How does potency relate to efficacy in case of first generation antipsychotic drugs?

First generation antipsychotics differ in potency but not in efficacy. For example, if haloperidol is more potent than chlorpromazine, it means that a lower dose of haloperidol is required to achieve the same therapeutic effect but chlorpromazine may be equally effective as haloperidol.

Qi. Explain why clinical response with antipsychotic treatment takes 3–4 weeks.

Treatment with antipsychotic drugs is aimed at decreasing the dopaminergic hyperactivity in the limbic system. Antipsychotic drugs not only block D2-postsynaptic receptors but also block D2-autoreceptor at the presynaptic nerve endings. D2-autoreceptor is inhibitory in nature and functions to inhibit the synthesis and release of dopamine. Immediate to the treatment, antipsychotic drugs antagonize the action of D2-autoreceptor and increases the release of dopamine but following repeated treatment they enter a state of physiological depolarization inactivation, with diminished production and release of dopamine, and this takes 3 to 4 weeks. Therefore, clinical response is seen over a period of 3 to 4 weeks.

Case Continued

After 6 months of treatment with olanzapine the patient came to the clinic for follow-up. The patient had shown some improvement in the symptoms and was feeling better. There was a weight gain of 4 kgs in 6 months. On interviewing her husband, he says there has been a sudden increase in her appetite and he has noticed her eating frequently. The blood and lipid tests show glucose and triglycerides at a higher range.

Qa. What could be the possible reasons for weight gain and derangement in blood glucose and lipid levels?

Atypical antipsychotics particularly olanzapine and clozapine have been reported to cause worse metabolic side effects including body weight gain, obesity, glucose dysregulation and hypertriglyceridemia.

Weight gain can be possibly due to antagonistic action of olanzapine at histaminic H1-receptor and 5-HT2A-receptor. Therefore, the patient should be counselled on her diet and exercise routine prior to and during treatment with olanzapine.

Atypical antipsychotic drugs can induce diabetes through multiple mechanisms:

1. Inhibition of insulin signalling pathway in the target cells such as muscle cells, hepatocytes and adipocytes to cause insulin resistance.
2. Antipsychotic drug-induced obesity can result in high levels of free fatty acids (FFA) and inflammation which can also cause insulin resistance.
3. Antipsychotic drugs can cause direct damage to beta-cells leading to dysfunction and apoptosis of beta-cells. Both insulin resistance and β-cell damage are factors for the development of diabetes.

In normal individuals, insulin inhibits breakdown of fat in adipose tissue leading to lipogenesis. Due to insulin resistance or insulin deficiency there is activation of lipoprotein lipase causing lipolysis and increased FFA generation. Increased free fatty acids enter the liver resulting in stimulation of triglyceride synthesis and hypertriglyceridemia.

Qb. Are there any atypical antipsychotics which are weight neutral? Enumerate.

Yes, the atypical antipsychotics which have lower risk of weight gain and dyslipidemia are ziprasidone, aripiprazole, asenapine and iloperidone.

Note: Molindone is an atypical antipsychotic which causes weight loss.

CASE 2: DRUG-INDUCED PARKINSONISM

A 62-year-old female patient CD from a poor family background was treated with oral haloperidol 15 mg/day for her psychiatric illness. Two months later, she presents to the clinic with complaints of abnormal muscle rhythmic movements of upper limb and lower limb, difficulty in walking. She has a stooped posture and takes small and fast steps.

CD was diagnosed with 'drug-induced parkinsonism'.

Qa. What is the neurological basis of the problem experienced by CD?

Drug-induced parkinsonism is due to antagonistic action of antipsychotic drugs at D2-receptors in the nigrostriatal tract. Dopamine deficiency leads to symptoms of akinesia, rigidity and tremor which is characteristic of Parkinson's disease.

Typical antipsychotics have predominant action on D2-receptors. Blockade of D2-receptors on the nigrostriatal tract probably relates to symptoms of parkinsonism.

Qb. Which drugs among the typical antipsychotics have least propensity for extrapyramidal side effects? Give reasons.

Typical antipsychotics or first generation antipsychotics such as chlorpromazine and thioridazine having less potent action on dopamine receptors of the brain are less likely to cause extrapyramidal side effects. Thioridazine, besides acting on dopamine receptors also acts on muscarinic receptors having prominent anticholinergic effects. This accounts for lower risk of extrapyramidal side effects.

Qc. Though thioridazine has lower risk of extrapyramidal side effects it is not used in common clinical practice. Give reasons.

i. Thioridazine has received a black box warning for its proarrhythmic clinical effects. It has been shown to cause QT-prolongation, especially in individuals on concurrent therapy with 2D6P450 isoenzyme antagonist which increases serum levels of the drug.

ii. An adverse effect which is distinctive to thioridazine is retinopathy in doses over 800 mg daily.

Qd. What are the treatment options available for drug-induced parkinsonism experienced in CD?

1. Reduce the antipsychotic dose if the patient does not destabilize with reduced dose.

2. Anticholinergics such as trihexyphenydyl, benztropine and benzhexol restore the balance between dopaminergic and cholinergic activities. Long-term use is associated with anticholinergic side effects, especially in elderly.
3. Amantadine which works through a separate mechanism may also be used in drug-induced parkinsonism.

Qe. Why levodopa or dopaminergic agonists are not used in drug-induced parkinsonism by antipsychotic drugs.

Antipsychotic drugs such as chlorpromazine have high binding affinity for D2-receptors and can induce parkinsonism due to antagonistic action at D2-receptors in the nigrostriatal tract. Therefore, dopamine precursor drugs such as levodopa are not useful in this setting because D2-receptors are blocked which prevents the actions of dopamine resulting in failure of therapeutic efficacy. Besides, the conversion of levodopa to dopamine may cause rise in dopamine levels leading to exacerbation of schizophrenia.

Case Continued

The patient CD was treated with amantadine for parkinsonian symptoms and gradually stabilized with a lower dose of haloperidol 6 mg/day. Five years later, the patient presents with complaints of restlessness, irregular movements of hands which decreased on holding an object or during other activities. The patient recognizing these symptoms as an adverse effect 'due to the drug', suddenly stopped taking haloperidol. Subsequently, there was worsening of the symptoms. She visited the psychiatric clinic for consultation. On physical examination, there was facial muscle contractions, lip smacking, tongue movements, twisting movements of the trunk.

The adverse effect was identified as tardive dyskinesia.

Qa. Explain the molecular mechanism leading to symptoms of tardive dyskinesia.

Tardive dyskinesia is commonly caused by typical antipsychotics which are highly potent D2-antagonists. Long term high level blockade of D2-receptors leads to upregulation or supersensitivity of postsynaptic dopamine receptors resulting in increased nigrostriatal dopaminergic activity with symptoms of tardive dyskinesia.

Qb. How would you treat tardive dyskinesia in patient CD?

Switching patients from typical antipsychotics to atypical antipsychotics which are associated with lower incidence of tardive dyskinesia. There are reports suggesting that atypical antipsychotics may have a beneficial effect on tardive dyskinesia remission. Clozapine and aripiprazole have proven to be effective in many cases.

CASE 3: DRUG-INDUCED HYPERPROLACTINEMIA

A 30-year-old female patient XY, on antipsychotic treatment with risperidone consults her psychiatrist regarding her menstrual problems, enlargement of breast and milk secretion from the breast. She complains that she has been experiencing these symptoms after dose of risperidone was increased in her last visit to the clinic.

Qa. What is the mechanism for hyperprolactinemia due to antipsychotics drugs?

Prolactin secretion is under tonic inhibitory control of dopamine. Therefore, prolactin is released when dopamine secretion is inhibited. Typical antipsychotic drugs have strong antagonistic action on D2-receptors, thus the inhibitory effects of dopamine on prolactin release is removed which results in hyperprolactinemia.

Qb. What are the effects of atypical antipsychotic drugs on prolactin levels when used in psychotic patients?

1. Most of the atypical antipsychotic drugs do not cause sustained hyperprolactinemia because of their lower affinity for D2-receptors.
2. In addition, serotonin is believed to be a modulator of dopamine secretion. Blockade of 5-HT2A-serotonin receptor leads to an increase in dopamine concentration which controls the levels of prolactin. Therefore, there is reduced risk of hyperprolactinemia.
3. Aripiprazole is an atypical antipsychotic drug. It is known to be a partial agonist at D2-receptors and an antagonist at 5-HT2A-receptor. Based on these properties, it can cause decrease in serum prolactin levels.

Qc. How would you treat symptomatic antipsychotic-induced hyperprolactinemia?

1. In symptomatic patients, dose reduction or switching to an agent with less potent D2-blockade is considered as first-line therapy.
2. If this is not possible due to clinical reasons, a dopamine agonist such as bromocriptine, cabergoline or amantadine may be considered.
3. There are studies which support the use of aripiprazole as an adjunctive treatment due to its unique property of decreasing serum prolactin in patient in whom switching from a potent agent to alternative treatment is not possible.

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Section VI

Chemotherapy of Microbial Diseases

17. Antimalarial Drugs
18. Antiviral Drugs
19. Antifungal Drugs
20. Antitubercular Drugs

Chapter

17

Antimalarial Drugs

CASE 1: DRUG THERAPY IN A CASE OF *P. VIVAX* MALARIA

A 40-year-old male JK, presented with history of fever, abdominal pain, nausea, vomiting and diarrhoea for last 5 days. Physical examination showed mild jaundice, no signs of bleeding, petechiae or rash, absence of hepatomegaly or splenomegaly. The patient was on symptomatic treatment with paracetamol.

Laboratory investigations showed haemoglobin levels of 9 g/dl, a platelet count of 90,000 per mm^3. Microscopic examination of Giemsa-stained blood smear showed trophozoites of *P. vivax*. Rapid diagnostic testing revealed a *P. vivax* infection. Liver function test and kidney function test were normal.

Qa. Explain the life cycle of malaria parasite.

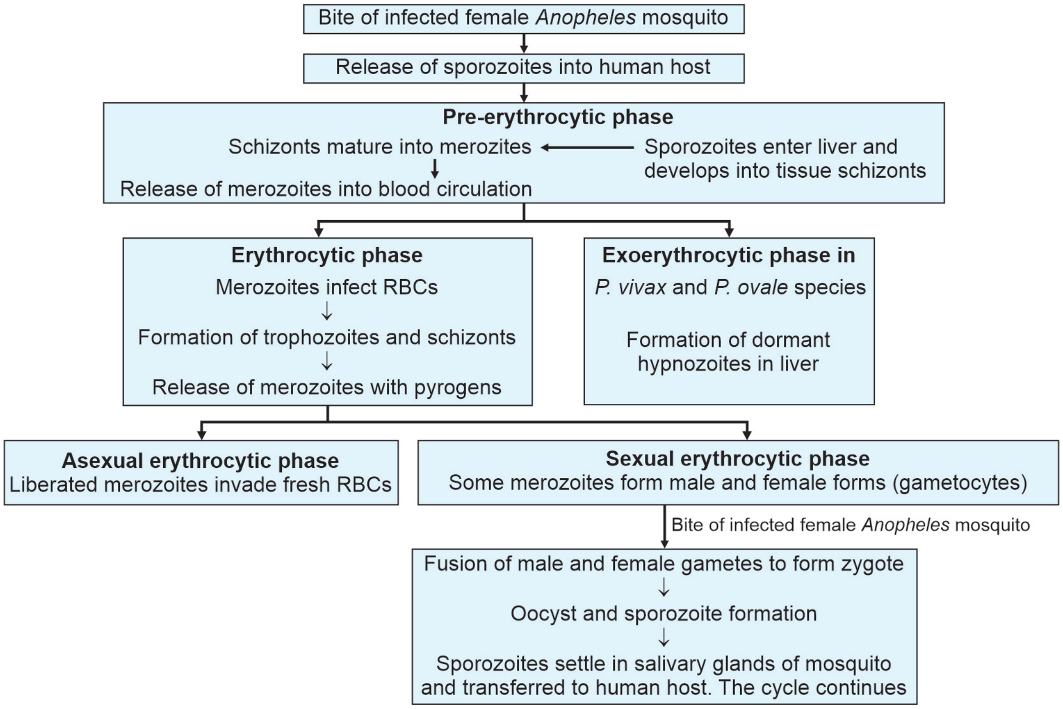

Bite of infected female *Anopheles* mosquito
Release of sporozoites into human host
Pre-erythrocytic phase
Schizonts mature into merozites
Sporozoites enter liver and develops into tissue schizonts
Release of merozoites into blood circulation
Erythrocytic phase
Merozoites infect RBCs
Formation of trophozoites and schizonts
Release of merozoites with pyrogens
Exoerythrocytic phase in
P. vivax and *P. ovale* species
Formation of dormant hypnozoites in liver
Asexual erythrocytic phase
Liberated merozoites invade fresh RBCs
Sexual erythrocytic phase
Some merozoites form male and female forms (gametocytes)
Bite of infected female *Anopheles* mosquito
Fusion of male and female gametes to form zygote
Oocyst and sporozoite formation
Sporozoites settle in salivary glands of mosquito and transferred to human host. The cycle continues

Fig. 17.1: Life cycle of malaria parasite

The life cycle of malarial parasite (*Plasmodium*) consists of sexual cycle which takes place in female anopheline mosquito (definitive host) and asexual cycle which occurs in human beings.

The female anopheline mosquito gets infected by biting a patient of malaria whose blood contains male and female gametes of the parasite. In the gut of the mosquito, male and female gametes fuse to form the zygote which develops into oocyst. The sporozoites are released from the oocyst which migrate to the salivary glands of the mosquito and stay there.

The sporozoites enter the human host by the bite of the female mosquito. The sporozoites can hardly survive in the circulation for long and hence these seek shelter in the liver parenchymal cells where they develop into schizonts which mature to form merozoites that are liberated into the circulation. This phase is known as ***pre-erythrocytic phase***.

After reaching the circulation the merozoites invade the red blood cells. This is followed by the formation of trophozoites and schizonts which undergo schizogony and release large number of merozoites, pyrogens and polymerised heme into the circulation by the rupture of the RBC. This phase which occurs in the RBC is known as ***erythrocytic phase***. The liberated merozoites further invade fresh erythrocytes and the ***asexual erythrocytic cycle*** starts again. Some merozoites, on entering the erythrocytes differentiate into male and female forms of the parasites called gametocytes. This is called the ***sexual erythrocytic phase*** of the life cycle. These gametes pass into the mosquito which undergo fertilization and eventually lead to the formation of sporozoites. The sporozoites reach the salivary glands and are transmitted to the human being on biting and the further cycle continues.

Some of the schizonts after the release from pre-erythrocytic schizogony phase re-enter liver and form dormant hypnozoites which may be reactivated later and cause relapse of malaria. This is known as ***exoerythrocytic phase*** and happens if the plasmodial species is *P. vivax* or *P. ovale*.

Qb. How are the antimalarial drugs classified on the basis of their antimalarial activity? Also mention the chemical classification of antimalarial drugs.

Antimalarial drugs	*Antimalarial activity*
Tissue schizonticides Primaquine and pyrimethamine	*For causal prophylaxis*: These drugs act on the primary tissue forms of the plasmodia, which after growth within the liver initiate the erythrocytic stage *For preventing relapse*: These drugs act on the hypnozoites of *P. vivax and P. ovale* in the liver that cause relapse of symptoms on reactivation
Blood schizonticides *Type 1: Fast acting, high efficacy drugs*—chloroquine, quinine, mefloquine, lumefantrine, artemisinin *Type 2: Slow-acting, low efficacy drugs*—sulfadoxine, pyrimethamine, proguanil	These drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria

Gametocytocides Primaquine (all 4 species of plasmodia) Chloroquine and quinine (all species except *P. falciparum*)	These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Primaquine has gametocytocidal activity against all species of *Plasmodium*. Chloroquine and quinine have gametocytocidal activity against all species except *P. falciparum*
Sporontocides Pyrimethamine, proguanil	These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission

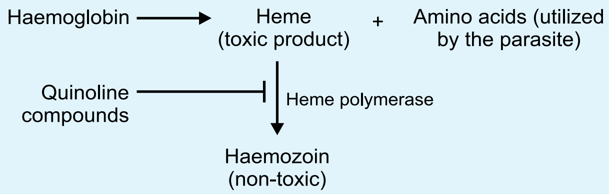
Classification of Drugs According to the Chemical Structure

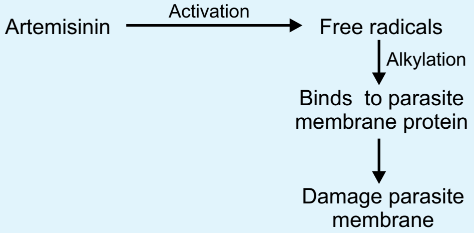
1. Aryl amino alcohols: Quinine, mefloquine, halofantrine.
2. 4-aminoquinolines: Chloroquine, amodiaquine.
3. Folate synthesis inhibitors:
   Type 1: Competitive inhibitors of dihydropteroate synthase-sulphonamides;
   Type 2: Inhibitors of dihydrofolate reductase-pyrimethamine, proguanil.
4. 8-aminoquinolines: Primaquine
5. Antimicrobials: Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones
6. Artemisinin derivatives and analogues-artemether, arteether, artesunate.
7. Napthoquinones: Atovaquone
8. Iron-chelating agents: Desferrioxamine

Qc. What are the aims of treatment of malaria?

Aims	*Causation*	*Therapy*
To alleviate symptoms	Symptoms are caused by blood forms of the parasite	Blood schizonticidal drugs
To prevent relapses	Relapses are due to hypnozoites of *P. vivax/P. ovale*	Tissue schizonticidal drugs
To prevent spread	Spread is through the gametocytes	Gametocytocidal drugs

Qd. How do the antimalarial drugs work in the treatment of malaria?

Drugs	*Mechanism of action*
Quinoline compounds (chloroquine, quinine, mefloquine)	**Inhibitors of heme metabolism** Heme polymerisation blocked by inhibiting heme polymerase enzyme resulting in accumulation of toxic heme causing damage to the parasite.  Haemoglobin Heme (toxic product) + Amino acids (utilized by the parasite) Quinoline compounds Heme polymerase Haemozoin (non-toxic)
Primaquine and atovaquone	**Inhibitors of electron transport chain** at the cytochrome complex in the parasite during respiration process

Doxycycline, tetracycline and clindamycin	**Inhibitors of parasite protein synthesis**
Sulfadoxine + Pyrimethamine	**Inhibitors of folate metabolism** by enzyme inhibition of DHFS (dihydrofolate synthetase) and DHFR (dihydrofolate reductase)
Artemisinin compounds: Artesunate, artemether, arte-ether	**Generation of free radicals which kills parasite**  Artemisinin Activation Free radicals Alkylation Binds to parasite membrane protein Damage parasite membrane

Case Continued

Treatment prescribed

Chloroquine phosphate: **Oral 1 g salt (600 mg base) at 0 hr (stat) followed by 0.5 g salt (300 mg base) at 6, 24 and 48 hrs. He was told to take 4 tablets together immediately, followed by 2 tablets after 6, 24 and 48 hours.**

He was also prescribed primaquine 15 mg/day for 14 days. She was also given acetaminophen 1,000 mg for her fever. She was monitored clinically and microscopy performed six hourly.

Qa. Explain why 4 tablets are being given stat followed by 2 tablets after 6, 24 and 48 hours for the treatment of vivax malaria.

Chloroquine has high tissue affinity and is widely distributed in the tissues. It has a large volume of distribution (100 to 1,000 litres/kg) and extremely long terminal half-life (30 to 60 days). These kinetic parameters suggest that a loading dose of chloroquine on the first day should be given in order to enhance the distribution of the drug. With this loading dose, effective steady state is achieved quickly and the steady state plasma level of the drug is maintained with subsequent doses of 300 mg base. Therefore, the initial dose of chloroquine is 600 mg base followed by 300 mg base at 6, 24 and 48 hours.

Qb. Why is oral chloroquine preferred over parenteral chloroquine?

Oral bioavailability of chloroquine is good. It is rapidly and almost completely absorbed from the gut. Following parenteral administration, toxic plasma concentration may be attained in a very short time. It is known that cardiac arrhythmias and hypotension may complicate such therapy. Parenteral administration of chloroquine should be avoided but when required may be given diluted in normal saline infused over several hours with a close watch over the blood pressure.

Qc. What is the rationale of using primaquine with chloroquine for the radical cure of vivax malaria? Is primaquine therapy necessary for radical cure of *P. falciparum* malaria?

Radical treatment is administration of primaquine to all confirmed cases of malaria.

In *P. vivax or P. ovale* malaria, primaquine provides radical cure of malaria by eliminating the hypnozoites (exoerythrocytic forms) of malarial parasite. Some of the schizonts released during pre-erythrocytic schizogony, re-enter the liver parenchymal cells and form dormant hypnozoites. This phase is called exoerythrocytic stage. The hibernation of hypnozoites may last for several months but these can be reactivated later to schizonts which release merozoites, that undergo erythrocytic schizogony leading to relapse of malarial fever. For *P. vivax* malaria, 2 weeks therapy with primaquine prevents relapses.

For radical cure of *P. falciparum* malaria, a single dose of primaquine destroys the gametocytes, thereby prevents the spread of the infection into the mosquito.

Qd. Primaquine should not be administered in G6PD deficient individuals and in pregnancy. Explain with reasons.

Primaquine induces oxidative stress by formation of numerous oxidised compounds. G6PD enzyme is needed to protect the erythrocytes against oxidative damage. It can cause haemolytic anaemia in G6PD-deficient persons. G6PD screening must occur prior to starting treatment with primaquine.

Primaquine should never be administered in pregnant woman because it crosses the placenta and can induce fatal haemolysis in fetal erythrocytes independent of maternal G6PD status.

Qe. Why is chloroquine used for the treatment of hepatic amoebiasis and not intestinal or luminal amoebiasis? Explain the rationale for its use in rheumatoid arthritis.

Chloroquine has activity against *Entamoeba histolytica.* It attains high concentration in the liver and is useful in hepatic amoebiasis.

Chloroquine has anti-inflammatory properties because of which it is used in rheumatoid arthritis as a disease modifying antirheumatic drug.

Qf. How does long-term use of chloroquine affect the retina? Is eye screening necessary for patients taking chloroquine?

Chloroquine has a high affinity for melanin rich tissues and nuclear chromatin. It thus accumulates in retina and cause damage to the retina. High dose and long duration of use are the most significant risks.

A baseline fundus examination should be performed to rule out pre-existing maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors. Patients should be informed about risk of toxicity, proper dose levels, and the importance of regular screening.

Case Continued

For the next three days, he continued to spike fever on the full chloroquine regimen and blood films remain positive for malarial parasite. His haemoglobin decreased progressively over the next 3 days to 7.5 mg/dl and his platelet count dropped to 50,000/mm^3. Drug resistance testing by molecular methods suggested chloroquine-resistant *P. vivax* malaria.

Qa. What are the treatment options of chloroquine-resistant vivax malaria as in case of JK?

1. Artemisinin combination therapy (ACT) is highly effective in the treatment of vivax malaria. ACT containing piperaquine, mefloquine or lumefantrine is the recommended treatment, although artesunate + amodiaquine may also be effective in some areas, or
2. Quinine sulphate alone or in combination with tetracycline or doxycycline or clindamycin.

CASE 2: DRUG THERAPY IN A CASE OF UNCOMPLICATED OR NON-SEVERE *P. FALCIPARUM* MALARIA

A 25-year-old female RY, attended the clinic with complains of periodic spiking fever, malaise, arthralgia, abdominal discomfort, nausea and vomiting. There was history of dry cough and on examination the respiratory rate was high. She was prescribed an antibiotic suspecting respiratory infection and tablet paracetamol and advised tepid sponging during fever. The patient came back after 5 days with no improvement in symptoms. On physical examination there were signs of pallor, icterus, tender hepatosplenomegaly, pulse 100 beats/min, BP was 110/70 mm of Hg.

Laboratory report revealed mild anaemia (normocytic normochromic type), thrombocytopenia. Microscopic examination of blood smear showed *P. falciparum* species. Liver function test showed mild rise in both conjugated and unconjugated bilirubin and moderately elevated LDH. Renal function test was normal.

RY was diagnosed as a case of *uncomplicated or non-severe falciparum malaria.*

Qa. Mention the ACT regimens recommended by WHO for the treatment of *P. falciparum* malaria.

One of the following ACTs can be used for the treatment of uncomplicated *P. falciparum* malaria:

- Artemether + Lumefantrine
- Artesunate + Mefloquine
- Artesunate + Amodiaquine
- Artesunate + Sulfadoxine-pyrimethamine (SP)
- Dihydroartemisinin + Piperaquine

Qb. What are the benefits of artemisinin-based combination therapies (ACTs)?

It is recommended that artemisinin compounds be coadministered with a second agent with a longer half-life and a different mechanism of action.

The short-acting but potent artemisinin component (i.e. artemether, artesunate, or dihydroartemisinin) reduce parasite numbers by a factor of approximately 10,000 in each asexual cycle which is more than other current antimalarials (which reduce parasite numbers 100 to 1000-fold per cycle). This causes rapid clearance of parasitaemia and rapid resolution of symptoms. It is then rapidly eliminated from the body. The longer acting partner drug (mefloquine, lumefantrine, piperaquine or amodiaquine) remains in therapeutically effective concentration in the blood till all the infecting parasites are killed and is responsible for complete clearance of the parasites. Artemisinin is active against all four species of malarial parasite and generally well tolerated.

The two drugs with different mechanism of action are likely to have different resistance mechanisms. So, combination therapy delays or slows the development of resistance.

Reduction of transmission of infection to the mosquitoes due to the effect of artemisinin derivatives on gametocyte forms of the parasite.

Therefore, the combination of artemisinin derivative with a second antimalarial agent is more effective, reduces transmission, prevents emergence of resistance to both drugs.

CASE 3: DRUG THERAPY OF MALARIA IN PREGNANCY

RY, a 32-year-old pregnant female, in her first trimester, was diagnosed with chloroquine sensitive vivax malaria.

Qa. Is it safe to initiate treatment with chloroquine in case of RY? How do the other antimalarial drugs affect pregnancy, given that RY is in her first trimester?

Chloroquine can be used safely in all trimesters of pregnancy. Artemisinin is not recommended for routine use in the first trimester, but can be safely used in the second and third trimesters. Quinine can be used in pregnancy, but one should be watchful about hypoglycaemia. Mefloquine is contraindicated in the first trimester of pregnancy.

Halofantrine, tetracycline and doxycycline are absolutely contraindicated in pregnancy. Primaquine is also contraindicated in pregnancy.

Qb. Why is it advisable to monitor blood glucose levels at least once 4–6 hours while quinine is administered?

Hypoglycaemia can be caused by quinine-induced insulin secretion in conjunction with increased consumption of glucose by the host and the growing parasites. This can be more severe in patients with severe infection and pregnancy. Hypoglycaemia in malaria may go unnoticed and could even cause death. All patients treated with intravenous quinine should receive a continuous infusion of 5 to 10 % dextrose to prevent hypoglycaemia. Therefore, it is advisable to monitor blood glucose levels at least once 4–6 hours while quinine is administered.

CASE 4: DRUG THERAPY OF SEVERE *P. FALCIPARUM* MALARIA

A 3-year-old girl KL, from malaria endemic region presented at the emergency department with history of convulsions, altered sensorium irregular high fever of 40°C, loss of appetite, abnormal behaviour for last 2 days. On examination, BP is low with systolic BP less than 65 mmHg. Blood smear examination suggests *P. falciparum* malaria.

Qa. What is the likely diagnosis of the patient KL? Explain the drug therapy in the treatment of the patient KL.

The clinical features such as irregular spikes in fever with altered mental status, generalized seizures and in addition, the patient being from a malarious area arouses strong suspicion of cerebral malaria.

Parenteral artemisinin derivatives, artesunate or artemether are the first line choice for the treatment of severe malaria. Treat adults and children with severe malaria with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once, a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT.

Treatment regimen for adults is as follows:

- Artesunate 2.4 mg/kg IV or IM stat followed by 1.2 mg/kg at 2 and 24 h and then daily or
- Artemether 3.2 mg/kg IM stat followed by 1.6 mg/kg per day or
- Quinine sulphate 20 mg of salt/kg by IV infusion over 4 h followed by 10 mg/kg infused over 2–8 hrs every 8 hrs.

CASE 5: DRUG THERAPY FOR MALARIA CHEMOPROPHYLAXIS

A company executive SK, has to make a business trip to West Africa for a period of 1 week. As a preventive measure he wishes to take chemoprophylaxis against malaria and takes consultation from the physician.

Qa. What are the factors determining the choice of antimalarial agent for chemoprophylaxis? What are the regimens used for malaria chemoprophylaxis?

The choice of drug for chemoprophylaxis depends on the travel destination, the duration of potential exposure to vectors, parasite resistance pattern, level and seasonality of transmission, age and pregnancy.

In areas of chloroquine-sensitive malaria: Chloroquine

In endemic areas of chloroquine-resistance malaria: Mefloquine, atovaquone-proguanil, doxycycline.

Regimens for Malaria Chemoprophylaxis

1. **Chloroquine (300 mg base weekly):** Start 1–2 weeks before entering the endemic area and continue for 4 weeks after leaving.
2. **Atovaquone (250 mg)–proguanil (100 mg):** 1 tab/day starting 1–2 days prior to exposure and continuing for 7 days after exposure.
3. **Mefloquine:** 250 mg weekly starting 1–2 weeks before entering an endemic area and ending 4 weeks after leaving.
4. **Doxycycline (100 mg):** Once daily starting 1 day before and ending 4 weeks after leaving (for areas with MDR P. f.)
5. **Primaquine (30 mg base):** Daily starting several days before exposure and continued for 7 days postexposure.

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Chapter

18

Antiviral Drugs

CASE 1: ANTIRETROVIRAL DRUG THERAPY

A 30-year-old male patient AB, presents with fever, headache, joint pain, sudden weight loss, rash and dizziness. On examination, there is presence of white patches in the mouth.

Past history is unremarkable except for the blood transfusion he had received 7 years back.

Personal history: **He has a good socioeconomic background.**

HIV infection was suspected and HIV test was ordered. Lab report shows a viral load of 10,000 copies per microliter and CD4-cell T lymphocyte count of 550 cells/µl.

Liver function tests, renal profile, complete blood cell count are in normal limits.

After counselling, the patient on the benefits and risks of antiretroviral therapy (ART), and the importance of adherence to treatment, the patient agreed to start treatment. Subsequently, treatment was initiated with antiretroviral drugs (tenofovir, emtricitabine and efavirenz).

Qa. How does HIV virus replicate? Indicate the target sites of antiretroviral drugs.

Retroviral replication includes, attachment, penetration, uncoating, replication, assembly and release. Different antiretroviral drugs act at different stages of HIV replication.

Attachment: HIV virus first has to attach to a CD4-cell. The proteins on the outer surface of the virus (called gp41 and gp120) connect with receptors on the surface of CD4-cell (usually the CD4 receptor and the CCR5 coreceptor). Maraviroc inhibits HIV-1 entry via CCR5 coreceptor interaction.

Penetration: Entry into the host cell occurs through endocytosis or fusion of the viral envelope directly with the host cell membrane. Enfuviritide is a fusion inhibitor, which interferes with penetration of HIV-1 in the cells.

Uncoating: Once inside the cell, the viral capsid is degraded and the viral nucleic acid is released which then becomes available for replication.

Replication, Assembly and Release:

- HIV protein called reverse transcriptase (RT) transcribes the viral RNA into DNA. Two different types of RT inhibitors block this process: (i) **nucleoside reverse**

transcriptase inhibitors (NRTIs), and (ii) **non-nucleoside reverse transcriptase inhibitors (NNRTIs).**

- The viral DNA is transported across the nucleus, where the HIV-protein integrase integrates the HIV DNA into the host's DNA. Drugs that block this process are called **integrase inhibitors**.
- The host's normal transcription machinery transcribes HIV DNA into multiple copies of new HIV RNA.
- Some of this RNA become the genome of a new virus, while the cell uses other copies of the RNA to make new HIV proteins.
- The new viral RNA and HIV proteins move to the surface of the cell, where a new immature HIV viral forms. Finally, the virus is released from the cell, and the HIV protein called protease cleaves newly synthesized polyproteins to create a mature infectious virus. Drugs that block this process are called **protease inhibitors**.

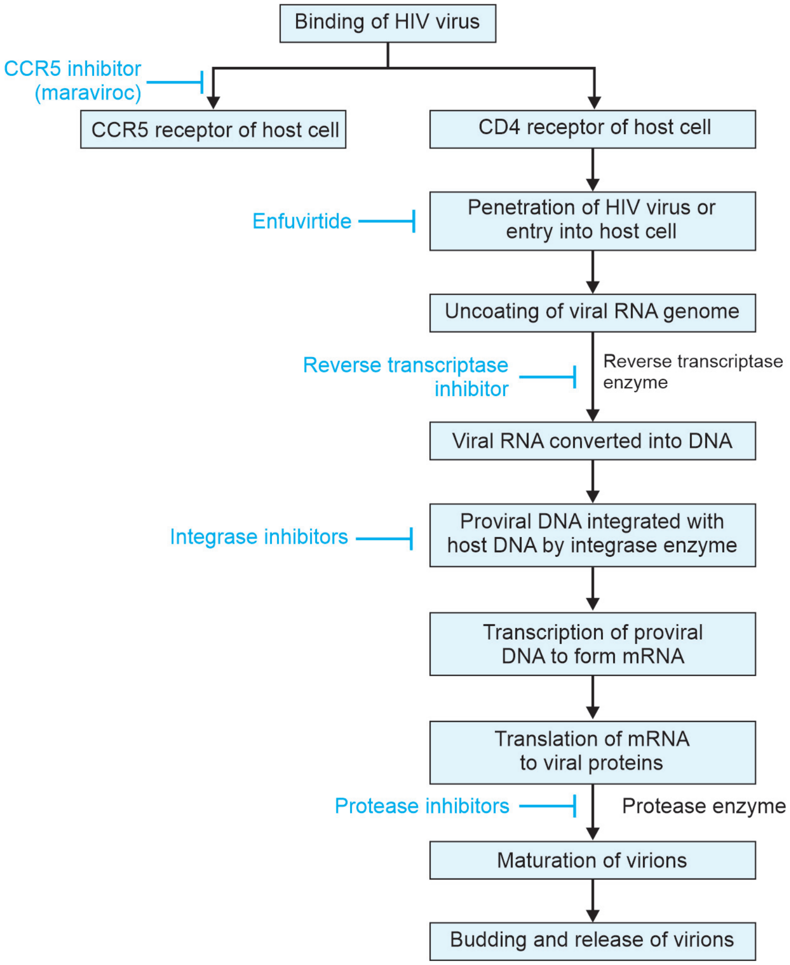
Binding of HIV virus
CCR5 inhibitor (maraviroc)
CCR5 receptor of host cell
CD4 receptor of host cell
Enfuvirtide
Penetration of HIV virus or entry into host cell
Uncoating of viral RNA genome
Reverse transcriptase inhibitor
Reverse transcriptase enzyme
Viral RNA converted into DNA
Integrase inhibitors
Proviral DNA integrated with host DNA by integrase enzyme
Transcription of proviral DNA to form mRNA
Translation of mRNA to viral proteins
Protease inhibitors
Protease enzyme
Maturation of virions
Budding and release of virions

Fig. 18.1: Replication of HIV virus and the target sites for antiretroviral drugs

The antiretroviral agents may be classified as:

Antiretroviral agents	
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine
Nucleotide reverse transcriptase inhibitors	Tenofovir disoproxil fumarate
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine, efavirenz and delaviridine
Protease inhibitors	Saquinavir, fosamprenavir, nelfinavir, indinavir, lopinavir, atazanavir, ritonavir, tipranavir and darunavir
Viral entry inhibitors	Enfuviritide
Integrase inhibitors	Raltegravir, dolutegravir
CCR5 inhibitors	Maraviroc

Qb. To which class of drug does tenofovir, emtricitabine and efavirenz belong to?

Tenofovir and emtricitabine belong to nucleoside reverse transcriptase inhibitors (NRTIs) and efavirenz is classified under non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Qc. What are the factors considered before deciding to initiate antiretroviral therapy?

It is important to consider the benefits, risks (both short term and long term), potential for the development of drug resistance and convenience in dosing regimens prior to initiating antiretroviral therapy (ART).

Qd. Considering the CD4–T-cell count and HIV viral load measurements of the patient AB, was it appropriate to initiate antiretroviral therapy?

AB has a viral load of 10,000 copies per microliter and CD4 cell–T lymphocyte count of 550 cells/µl. CD4–T-cell count and HIV viral load measurement are indicators to 'stage' the severity of infection. It is important to note that, as per the WHO guidelines, antiretroviral therapy should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4-cell count.

Evidence suggests, early initiation of treatment in patients with CD4 counts of >500 cells/µl improves immune recovery, reduces HIV transmission risk and potentially reduces the risk of AIDS (opportunistic infections) and non-AIDS defining conditions (including cardiovascular diseases, kidney diseases, liver diseases, several types of cancers and neurocognitive disorders). This reduces mortality and morbidity in the patient, thus improving the quality and duration of life.

Therefore, after discussing with the patient, the benefits and risks of drug therapy, the patient AB was motivated to undergo treatment of HIV infection. Treatment was initiated with antiretroviral drugs (tenofovir, emtricitabine and efavirenz).

Qe. State the clinical situations which favour immediate initiation of antiretroviral therapy in patients with HIV disease.

The clinical situations which favour immediate initiation of therapy in patients with HIV disease are the following:

- As a priority, ART should be initiated in all adults living with HIV with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4).
- Adults with CD4-cell count less than 350 cells/µl

- Pregnancy
- AIDS-defining condition such as an opportunistic infection
- HIV-associated nephropathy (HIVAN)
- Hepatitis B and/or C co-infection
- Rapidly declining CD4-cell count (>100 cells/µl decrease per year)

Qf. What are the initial combination regimens for a patient diagnosed with HIV infection?

Treatment is usually started with a combination of two NRTIs and a third drug. The third drug that is paired with two NRTIs is either a NNRTI, a ritonavir-boosted protease inhibitor or an integrase inhibitor.

Qg. Justify the selection of tenofovir and emtricitabine over other drugs of NRTI class, for combination therapy as a part of antiretroviral therapeutic regimen in patient AB.

New generation NRTIs (tenofovir and emtricitabine) when compared to older NRTIs (zidovudine and lamivudine) are considered to have *superior efficacy in terms of virologic suppression and CD4–T-cell response.*

The newer NRTIs in contrast to older generation NRTIs have low affinity for human DNA polymerase gamma, a mitochondrial enzyme, with lesser incidence of anaemia, granulocytopenia, myopathy, peripheral neuropathy and pancreatitis. This accounts for *better safety profile* of tenofovir and emtricitabine compared to other NRTIs.

In terms of *convenience,* the three drugs (tenofovir, emtricitabine and efavirenz) are coformulated in a single pill taken once daily. This improves compliance with the drug regime and reduces the potential for drug resistance and treatment failure.

Qh. How should the effectiveness of antiretroviral therapy be monitored in an HIV-infected patient treated with antiretroviral drugs?

Three important criteria determining the effectiveness of an antiretroviral regimen are the following:

1. **Clinical assessment:** In patients who are clinically symptomatic, resolution of clinical symptoms and improvement in the overall wellbeing might indicate the effectiveness of the antiretroviral therapy.
2. **Surrogate marker responses, viral load and CD4–T-cell measurements** serve as a useful guide regarding the effectiveness of ARV therapy. There is a rapid decrease in viral load by 4 to 8 weeks and it continues to decline in next 12 to 16 weeks and becomes undetectable. Repeat T-cell counts should be obtained at 3–4-month intervals once therapy is initiated.
3. **Regimen tolerability,** including a patient's ability to adhere to the regimen. If the ARV regimen selected for the patient produces intolerable side effects there is high likelihood of poor adherence to the regimen which might lead to treatment failure. Therefore compliance with the treatment regimen will determine the response to treatment.

Qi. How do the nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) act on the HIV replication cycle?

Nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) interrupt the HIV replication cycle via inhibition of HIV reverse transcriptase and termination of the DNA chain.

Reverse transcriptase is an HIV-specific DNA polymerase that allows HIV RNA to be transcribed into double strand proviral DNA and incorporated into the host cell genome.

Proviral DNA chain elongation is necessary before genome incorporation can occur and is accomplished by the addition of purine and pyrimidine nucleosides to the 3′-end of the growing chain.

Qj. What are the differences in the action of nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI), used as antiretroviral agents?

Nucleoside reverse transcriptase inhibitors (NRTIs) *competitively* inhibit the binding of incoming native nucleotides and block the replication of viral genome and results in premature chain termination. NNRTIs on the other hand are *not competitive*. They allosterically inhibit reverse transcriptase *by inducing a conformation change in the enzyme* that significantly reduces the rate of nucleotide transfer and chain elongation and prevent transcription of RNA to DNA.

Nucleoside reverse transcriptase inhibitors (NRTIs) *undergo phosphorylation* for their action on the reverse transcriptase enzyme. NNRTIs on the other hand *do not require phosphorylation* for activity.

Qk. Mention the limitations of nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) over protease inhibitors used for the treatment of HIV infection.

Nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) inhibit *the early stages of HIV replication life cycle*. Protease inhibitors on the other hand, directly bind to the catalytic site of HIV protease, inactivating the enzyme and preventing maturation of the HIV virion *occurring late in virion development*.

As a result, protease inhibitors inhibit viral replication in any infected cell regardless of the current stage of HIV replication within that cell. In contrast, reverse transcriptase inhibitors provide no benefit for those infected cells that are actively producing new strains of virus.

They can only protect newly infected cells from becoming latently infected cells before the formation and insertion of proviral DNA into the host cell’s genetic material.

Ql. Explain the reasons why protease inhibitors are not a part of initial treatment and are reserved for failure cases of HIV patients.

Protease inhibitors are not preferred *in the initiation of treatment of HIV patients* because of certain undesirable pharmacokinetic features which are the following:

- Variable and/or limited oral bioavailability and a short elimination half-life, which may lead to subtherapeutic systemic exposure. Low systemic exposure to PIs may result in exacerbation of viral resistance and decrease in treatment success.
- Large pill burden (increase in the number and frequency of dosage units, the patient must take each day) in order to achieve adequate blood concentrations to function as an effective antiHIV therapy. This may contribute to poor medication adherence.
- Extensive metabolism of PIs by cytochrome 3A4 (CYP3A4) which increases the potential for drug–drug interactions.

Protease inhibitors are reserved for the treatment of HIV failure cases because they have high genetic barrier and hence need long-term exposure before resistance emerges. Selection of multiple mutations in a viral strain is required for the development of resistance.

Qm. Compare the advantages and drawbacks of efavirenz and nevirapine.

Non-nucleoside reverse transcriptase inhibitors such as nevirapine and efavirenz are key drugs of highly active antiretroviral therapy (HAART) in the clinical management of acquired immune deficiency syndrome (AIDS)/HIV infection.

The advantages and drawbacks of efavirenz are the following:

Advantages:

- Efavirenz is highly potent.
- It has a long steady state half-life which protects the drug from frequent missed doses.
- It is available as a one-pill-once a day combination regimen.

Drawbacks:

- Efavirenz-treated patients experience neurological and neuropsychiatric reactions which range from transitory effects, such as nightmares, dizziness, insomnia, nervousness and lack of concentration, to more severe symptoms including depression, suicidal ideation or even psychosis.
- It is avoided in women with child-bearing potential because teratogenic effects are associated with its use.
- It is more expensive compared to nevirapine and is preferred in resource-rich areas.

Advantages and drawbacks of nevirapine:

- Used in resource-limited regions because of its low cost.
- It is less potent and more toxic than efavirenz. For unclear reasons, *nevirapine-related hepatotoxicity* is common in patients starting therapy with high CD4–T-cell count. So, nevirapine is generally not recommended for women who have a CD4–T-cell count higher than 250 cells per µl, or men who have a CD4–T-cell count higher than 400 cells per µl.

Qn. What could be the possible reason for the selection of efavirenz over nevirapine in the clinical management of the patient AB?

Efavirenz is preferred over nevirapine because of the following reasons:

- Personal history of AB suggests, he is from good socioeconomic background and can afford treatment with efavirenz.
- Efavirenz has substantial evidence of foetal risks and so caution is necessary when prescribed in women of child-bearing age. It can safely be prescribed in a male patient as the case of AB.
- The CD4-cell count of AB is higher than 400 cells per µl which increases the chances of nevirapine-related hepatotoxicity and thus efavirenz is a better alternative to nevirapine.

Qo. What is the most common reason for discontinuation of treatment with protease inhibitors in HIV-treated patients?

Protease inhibitors are most commonly associated with metabolic abnormalities such as peripheral fat wasting (lipoatrophy) and central fat accumulation (lipohypertrophy). These potentially disfiguring body changes can cause stigma and might be a major reason why most individuals delay or stop therapy.

Qp. Mention the clinical conditions in which the use of protease inhibitors is contraindicated.

Protease inhibitors may be less favoured with an existing medical condition consisting of coronary artery disease, hyperlipidaemia or diabetes mellitus because of their potential risk for metabolic side effects.

Qq. What is the rationale for combining low subtherapeutic dose of the protease inhibitor ritonavir, to a therapeutic dose of a second protease inhibitor?

Of the protease inhibitors, ritonavir is the most potent inhibitor of CYP3A4 and is used more often as *a low-dose pharmacokinetic booster* rather than in therapeutic doses as the primary protease inhibitor.

Protease inhibitors have short serum half-lives. Ritonavir has a remarkable capacity to inhibit CYP3A4 activity and thereby reduces first pass metabolism and hepatic clearance of the primary protease inhibitor extending its elimination half-life. Thus, the addition of low-dose ritonavir improves pharmacokinetic variability, resulting in more consistent serum concentrations throughout the dosing interval and improved treatment response.

Protease inhibitor boosted with ritonavir contributes to lower pill burden, which enhances medication adherence thus reducing the development of viral drug resistance and improving treatment success.

In addition, ritonavir inhibits P-glycoprotein (P-gp), a transmembrane efflux protein that transports protease inhibitor out of cells. This may increase penetration of protease inhibitors into viral sanctuary sites increasing the effectiveness of the primary protease inhibitor.

CASE 2: TREATMENT FAILURE TO ANTIRETROVIRAL DRUG REGIMEN

The patient AB responded well to the treatment regimen and there were no drug-related problems. His symptoms improved and he felt more energetic. He remained on the same treatment for 2 years. His T-cell count remains stable at 550 cells/µl and his viral load measurements have remained less than the limit of assay detection in her recent follow up visits.

After few years, he presents to the clinic with new complaints of fever, night sweats and malaise. There are visual problems of floating spots, light flashes and visual blurring.

AB states that he has been compliant with therapy and has not started any new medications. His current lab tests show viral load of 70,000 copies/ml and his CD4–T-cell count is 40 cells/µl (both repeated and validated).

In fundus examination, he had signs of retinal vasculitis. He is known to have a positive CMV IgG antibody titre. Renal profile and CBC count is normal.

The patient AB was diagnosed as a case of 'treatment failure' to antiretroviral drug regimen.

Qa. How do you define 'treatment failure'? What are the likely reasons for treatment failure?

'Virological treatment failure' is defined as *persistently detectable plasma HIV RNA concentrations after 16–24 weeks of therapy.*

Virological failure is mostly attributed to non-adherence or pre-existing drug resistance.

'Immunological treatment failure' arises when *CD4 recovery is inadequate* to protect the patient against AIDS and non-AIDS-related morbidity. The optimum immunological outcome seems to be sustained CD4–T-cell count in the normal range (more than 500 cells/µl).

Immunological failure is most common when treatment begins at a very advanced disease stage, e.g. CD4-cell count lower than 200 cells per µl. Old age increases the risk of immunological failure.

Qb. Why do you think AB is a case of 'treatment failure'?

The patient AB who was clinically stable with the prescribed regimen suddenly deteriorated with the new onset of constitutional symptoms such as fever, malaise and weakness. His CD4–T-cell count has declined to 40 cells/µl and viral load measurements increased to 70,000 copies/ml despite his adherence to ARV treatment regimen. So, this is possibly a case of *treatment failure* and immediate change in therapy is warranted.

Qc. How do you assess failure of antiretroviral treatment regimen?

The failure of antiretroviral treatment regimen is assessed based on the following parameters:

1. *Clinical symptoms*: Increase in constitutional symptoms or new onset of infection might suggest failure to treatment.
2. *Increase in viral load and decreased CD4–T-cell count:* Indicates viral replication and destruction of CD4–T-cell with regimen failure.

(Note: Other causes of increase in viral load including vaccinations and other concurrent infections should be ruled out during discussion with the patient.)

3. *Regimen tolerability and adherence:* Toxic side effects including drug–drug interactions associated with antiretroviral drugs and large pill burden are likely to cause doses to be missed or non-adherence to the antiretroviral regimen. This increases the possibility of emergence of drug resistance and treatment failure.

Qd. Should the antiretroviral treatment regimen be changed? If yes, explain with reasons.

Yes, change in the antiretroviral treatment regimen is necessary for an HIV patient who has failed therapy. This is because ongoing or prolonged viral replication in the presence of antiretroviral agents leads to the accumulation of resistance mutations which may limit future treatment options. So, the changes to therapy should occur close to the time of treatment failure.

Qe. What should the physician consider when changing the antiretroviral treatment regimen in case of failed therapy?

1. The new regimen should contain *at least two preferably three fully active antiretroviral agents.*
2. While choosing the new regimen, *the potential for cross-resistance between antiretroviral drugs should be considered*. Therefore, resistance testing is recommended.
3. If an agent in a given regimen is stopped, it is recommended that all agents in the regimen must be stopped, and restarted simultaneously to prevent the development of resistance.

[**Note:** An exception to this rule is when, components of a regimen have differing half-lives, example NNRTIs having longer half-life than NRTI. In this situation, if all drugs are discontinued simultaneously, continued monotherapy exposure with NNRTI results because of the longer half-life of NNRTI. This is the reason why some experts recommend continuing the NRTIs for 1 to 2 weeks, past-NNRTI discontinuation to provide combination therapy, while the NNRTI is eliminated from the body (covering the 'tail' of the pharmacokinetic profile).]

Qf. What is 'immune reconstitution inflammatory syndrome (IRIS)'?

'Immune reconstitution inflammatory syndrome (IRIS) can be defined as a paradoxical clinical worsening of a known condition or the appearance of a new condition *after initiating antiretroviral (ART) therapy* in HIV-infected patients, resulting from *restored immunity to specific infectious or non-infectious antigens.*

In patients with advanced HIV disease (i.e. CD4 <100 cells/µl), *immune dysfunction may occur,* resulting in an inability to mount an appropriate response to subclinical infections.

As a result, these infections replicate unimpeded and is often undetected by the host (also known as quiescent disease).

In such patients, dysregulated immune response may cause worsening of an existing infection or appearance of a new infection or disease process and inflammation occurring at the site of infection. The immune reconstitution inflammatory syndrome (IRIS) can present in any organ system where quiescent disease exists (e.g. CNS, eyes, lymph nodes) and exacerbate the clinical situation.

Qg. How do you differentiate 'immune reconstitution inflammatory syndrome (IRIS)' from 'clinical failure'?

'Clinical failure' is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given for sufficient time to induce a protective degree of immune restoration.

Clinical failure is differentiated from immune reconstitution inflammatory syndrome (IRIS) which can be seen *within the first several weeks after the institution of therapy* if a subclinical infection is present at baseline.

Failure of ART is characterized by *decrease in CD4+–T- cell count, increase in viral load* along with clinical deterioration and opportunistic infections. Whereas IRIS may be due to restoration of immunity suggested by *increased CD4+–T-cell count and decrease in plasma RNA level* after HAART.

Qh. As a clinician, what are the precautions to be taken for immune reconstitution inflammatory syndrome (IRIS) when ART is instituted in a patient with advanced HIV disease?

Patients who are started on ART having CD4+ count of less than 100 cells/µl require close clinical monitoring during the first weeks of ART.

Similarly, they should be counselled about the risk of development of IRIS to avoid being discouraged and defaulting on therapy as development of IRIS suggests increase in the immunity and is a good sign unless life-threatening.

Clinicians need to remain vigilant when initiating ART and individualize therapy according to known treatment options for the specific infectious agent.

Qi. Enumerate the drugs used for the treatment of CMV infection.

Ganciclovir, valganciclovir, foscarnet, cidofovir and fomivirsen are used for the treatment of CMV infection.

Qj. AB received intravitreal ganciclovir with good response to treatment. What is the mechanism of action of ganciclovir and why is it preferred to acyclovir in the treatment of CMV infection?

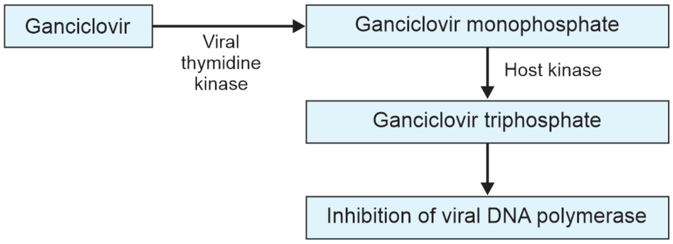

Fig. 18.2: Mechanism of action of ganciclovir

Ganciclovir has greater antiCMV activity compared to acyclovir. This is because intracellular ganciclovir triphosphate reaches a concentration of 10-fold higher than those of acyclovir triphosphate, and declines much more slowly with an intracellular elimination half-life of more than 24 hours. Due to long half-life, it is administered as a single daily dose.

Qk. What is the most important dose-limiting toxicity of ganciclovir?

Bone marrow suppression is the principal dose-limiting toxicity of ganciclovir with neutropenia occurring in approximately 50% of patients. Thrombocytopenia is also observed. Absolute neutrophil counts (ANCs) and platelets should therefore be monitored weekly during ganciclovir therapy.

Ql. Mention two antiviral drugs that can be used in the treatment of resistant CMV retinitis.

Foscarnet and *cidofovir* are the two antiviral drugs that can be used in the treatment of resistant CMV retinitis. In contrast to ganciclovir, foscarnet and cidofovir do not require viral kinases for phosphorylation and thus activity is maintained against kinase deficient viral mutants that are resistant to ganciclovir. Both are available as intravenous formulation because oral bioavailability is poor.

Qm. What is the main organ toxicity associated with foscarnet and cidofovir? What preventive measures can be taken against it?

The primary adverse effect common to foscarnet and cidofovir is nephrotoxicity.

To prevent nephrotoxicity, the following measures are taken:

- Concurrent administration of other potentially nephrotoxic drugs (e.g. amphotericin B, aminoglycosides, non-steroidal antiinflammatory drugs, pentamidine, foscarnet) should be avoided.
- Also adequate IV prehydration with 0.9% sodium chloride should be maintained.
- Probenecid is administered concomitantly with cidofovir to prevent nephrotoxicity. It blocks tubular transport and reduces renal clearance and associated nephrotoxicity. However, the use of probenecid may be associated with drug–drug interaction and other toxicities.

CASE 3: DRUG THERAPY OF HEPATITIS B INFECTION

A 45-year-old female patient 'PR', presents to emergency department with complaints of intermittent vague abdominal pain, decreased appetite, fatigue for last one month. Few days ago she noticed yellowing of eyes and darkening of urine.

On examination, abdomen is soft, liver is enlarged, non-tender and smooth. The spleen is palpable. The cardiac, pulmonary and neurologic examinations are normal. She is afebrile and her blood pressure, heart rate and respiratory rate are within normal limits.

Patient's social history suggests, he was an addict of heroin. Laboratory investigations suggest hepatitis serologic tests positive for HBsAg, HBeAg, hepatitis viral DNA is 30,000 IU/ml, bilirubin 3.2 mg/dl, AST 318 units/L, ALT 378 units/L, liver biopsy reveals periportal inflammation as well as piecemeal and bridging necrosis.

Your diagnosis: **Chronic hepatitis secondary to hepatitis B.**

Qa. Does the patient 'PR' require antiviral therapy for chronic hepatitis secondary to hepatitis B?

The clinical symptoms together with jaundice, hepatosplenomegaly and elevated liver enzymes (AST and ALT enzymes) indicate chronic hepatitis. Presence of HBsAg and HBeAg, significantly elevated levels of hepatitis B viral DNA (>20,000 IU/ml) and liver enzymes (AST and ALT) are suggestive of ongoing viral replication and high infectivity. Therefore, antiviral therapy is required to slow the progression of chronic hepatitis to cirrhosis, reduce incidence of liver cancer and improve long-term survival.

Qb. What are the goals of therapy?

The goals of therapy in chronic HBV infection are suppression of active viral replication as indicated by disappearance of detectable HBeAg and HBV DNA. This is associated with a reduction in inflammatory cells within the liver, and a fall of serum aminotransferases.

Qc. Enumerate the drugs for the treatment of chronic hepatitis B.

Tenofovir, entecavir, interferon alfa, pegylated interferon alfa-2a, adefovir, telbivudine are used for the treatment of chronic hepatitis B.

Qd. How does IFN-α act in the treatment of chronic hepatitis B?

Interferons bind to specific cell surface receptors, and induce synthesis of effector proteins, which produce antiproliferative, antiviral and immunomodulatory actions. Their antiviral activity possibly arises from their ability to inhibit viral entry into the host cells and modulate several steps of the viral replication cycle (e.g. viral uncoating, inhibition of messenger RNA, and protein synthesis).

Qe. How is PegIFN-α better than IFN-α in the management of chronic hepatitis B?

Pegylated IFN (PegIFN-α2a, Pegasys) is the only FDA-approved interferon (IFN) for the treatment of chronic HBV infection. The addition of polyethylene glycol to IFN leads to increased serum half-life, resulting in a prolonged antiviral effect which reduces the frequency of administration of interferon from three times weekly to once a week subcutaneously. Clinical data suggests that pegylated IFN has slightly enhanced efficacy than standard IFN formulations.

Qf. Should you consider interferon-based treatments in patients with advanced liver disease safe as in case of PR which is case of decompensated liver disease? Explain.

Interferon-based treatments have a poor safety profile and limited efficacy in patients with advanced liver disease. In patients with high (>2 times the upper limit of normal) pretreatment aminotransferase levels, HBV DNA greater than 20,000 IU/ml, and long duration of chronic hepatitis, treatment with pegylated IFN (PegIFN-α2a) may lead to suboptimal response.

Qg. Which antiviral drugs could be used in case of PR, a case of chronic hepatitis secondary to hepatitis B? Discuss the use of antiviral drugs in chronic hepatitis B infection.

For patients with decompensated liver disease as in case of patient 'PR', entecavir or tenofovir should be offered as first-line treatment instead of PegIFN due to the high risk of serious infections and hepatic failure.

Tenofovir and entecavir are the most potent drugs with high efficacy to suppress hepatitis B virus. They have high barrier to resistance and rarely lead to drug resistance compared with other drugs, are simple to take (1 pill a day) and have few side effects so require only limited monitoring. Therefore, numerous guidelines recommend the use of oral tenofovir or entecavir as first-line therapy in the treatment of chronic active hepatitis B.

Telbivudine, lamivudine and adefovir are considered as second- or third-line antiviral therapy. *Telbivudine* appears to have slightly more potent antiviral activity than do adefovir and lamivudine but it is more expensive and plays a limited role in primary therapy. *Lamivudine's* role in hepatitis B infection is diminishing as alternate therapies become available. Another disadvantage to this therapy includes its high rate of drug resistance. Patients on *Adefovir* must have their kidney monitored regularly because the primary adverse effect of adefovir is nephrotoxicity.

CASE 4: DRUG THERAPY OF INFLUENZA

A 60-year-old male was admitted to the hospital with symptoms of lethargy, high fever, shortness of breath and non-productive cough. Investigations detected H1N1 infection. CT scan revealed interstitial pneumonia.

He was treated with oseltamivir, prednisone and antibiotic therapy consisting of ceftriaxone and azithromycin.

His respiratory function improved slowly and symptoms of fever, cough improved and the patient was discharged in 2 weeks.

Qa. Enumerate the drugs available for the treatment of influenza.

Amantadine, rimantadine, oseltamivir and zanamivir are used as drug therapy for influenza.

Qb. How does oseltamivir act in the treatment of infection with influenza?

Oseltamivir inhibits the neuraminidase enzyme, which is expressed on the viral surface. The enzyme promotes release of virus from infected cells and facilitates viral movement in the respiratory tract.

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Chapter

19

Antifungal Drugs

CASE 1: DRUG THERAPY OF ONYCHOMYCOSIS

A 30-year-old female AB, presented to the dermatology out-patient department with brownish black discoloration of the nails of the right index and middle finger of the right hand. On examination, the finger nails were yellowish brown in color with loss of texture and there were dystrophic changes and onycholysis in the affected nails. The subungual region was thickened with mild inflammation.

Microscopic examination revealed filamentous hyphae compatible with a dermatophyte infection. A diagnosis of *Tinea unguium* (onychomycosis) was made.

Ultramicrosized griseofulvin was administered orally at 10 mg/kg/day in single daily dosing for 6 months.

Qa. Which is the causative organism in the clinical case described above? How does griseofulvin act in the treatment of tinea infection of the nail (onychomycosis) as it is used in case of AB?

Distal subungual onychomycosis is usually caused by the dermatophyte *trichopyton rubrum* and is confirmed with microscopic examination and culture.

Griseofulvin has high affinity for keratin precursor cells and attains high concentration in differentiated cells such as skin, hair and nails. It is fungistatic in nature and acts by inhibiting fungal mitosis by binding to tubulin, a microtubule-associated protein, thereby disrupting the assembly of the mitotic spindle and fungal multiplication. The prolonged and tight association with keratin allows new growth of skin, hair or nail to be free of dermatophyte infection. Therapy should be considered successful when several millimeters of healthy nail have emerged from the nailfold to the margin of infected nail or when a 25% reduction in the size of the infected site has been achieved.

Qb. What instructions would you give to AB, who is on griseofulvin therapy?

- While taking griseofulvin, alcohol containing drinks should be avoided because some of the ethanol effects can be increased by griseofulvin and the patients may experience flushing, tachycardia and excessive sweating.
- It is best to take griseofulvin with a meal because absorption may be enhanced by concomitant intake of high fat meal.
- Griseofulvin should not be used with other medicines such as warfarin or oral contraceptive pills because it is an inducer of cytochrome P450 enzymes which results in increased metabolism and reduced efficacy of warfarin or oral contraceptive pills.

- Griseofulvin is known to cause fetal malformations and it should not be used if a woman is pregnant or planning to become pregnant.

For dermatophyte nail or paronychial infections, griseofulvin therapy could be used if an azole or allylamine is contraindicated

Qc. Which drugs are better alternatives to griseofulvin? How are they superior to griseofulvin in the management of onychomycosis?

Itraconazole, an azole derivative or terbinafine, an allylamine are safe and better alternatives to griseofulvin in the management of onychomycosis.

Terbinafine and itraconazole have the following advantages over griseofulvin:

a. Terbinafine and itraconazole quickly produce high drug levels in the nail, which persists after therapy is discontinued.
b. Itraconazole has a broader spectrum of coverage.
c. Side effects and drug interactions are less common with terbinafine or itraconazole.
d. Shorter duration of treatment which is 3 months with terbinafine or itraconazole compared to griseofulvin for which the treatment is 12–18 months.
e. Cure rate of ≥75% have been achieved with both drugs, while griseofulvin produces a cure rate of 50% and a relapse rate of 50% after 1 year.

CASE 2 : DRUG THERAPY OF TINEA CAPITIS (TC)

A 12-month-old infant presented to a pediatrician with complaints of erythematous lesions and annular patches on the scalp along with hair loss. The infant was in good health with no history of recent illness or any animal contact.

Investigations: Wood's light examination, fungal culture of the scalp lesions, microscopic examination of the culture indicates infestation by *Microsporum canis* resulting in tinea capitis.

Qa. Which drugs would you recommend for the treatment of tinea capitis in children?

Tinea capitis is a fungal infection in which topical therapy is unsuccessful. Till date, the use of oral antifungal therapy is the first-line treatment for the management of tinea capitis (TC). *Griseofulvin* remains the gold standard for effective management of TC. It offers a long-term safety and proven efficacy, provided the dose is used on the basis of weight and administered for an appropriate duration. *Oral terbinafine* is a safe and effective alternative to griseofulvin in treating tinea capitis in children.

Qb. How does terbinafine (allylamine) and itraconazole (azole group) produce antifungal effect?

Terbinafine acts by inhibiting the enzyme squalene epoxidase, thereby inhibiting ergosterol synthesis.

Itraconazole blocks cytochrome P450-mediated lanosterol demethylation to ergosterol, the principal sterol of fungal membrane. So, the function of fungal membrane is interrupted and the permeability is increased.

CASE 3: AMPHOTERICIN USE FOR THE MANAGEMENT OF INVASIVE CANDIDIASIS

CD, a 55-year-old male was admitted to the hospital with complaints of nausea, vomiting and epigastric pain after alcohol binge. The patient is a known case of diabetes, hypertension and alcohol use disorder. Pancreatic necrosis was diagnosed on the basis of results of CT scan of abdomen requiring percutaneous drainage. Subsequently, he

developed fever of 39°C and chills. His blood pressure had dropped more than 30 mmHg systolic. IV piperacillin/tazobactum was started. Despite 3 days of antibiotic use, he remains febrile. Blood culture report revealed *Candida glabrata* species.

IV amphotericin-B 5 mg/kg was used for empirical treatment of invasive candidiasis.

Qa. Explain the mechanism of action of amphotericin-B.

Amphotericin-B has higher affinity for ergosterol than cholesterol and binding of amphotericin B to ergosterol forms pores or channels in the fungal membrane, increasing the permeability resulting in leakage of essential cellular contents and ultimately leading to cell death.

Amphotericin-B also causes damage to fungal membranes by toxic free radicals generated by oxidation of the drug.

Case Continued

During amphotericin-B infusion, CD complains of headache, fever with chill and rigor for last 2 days.

Qa. What is the possible reason for the symptoms experienced by CD on being administered with amphotericin-B infusion?

Administration of amphotericin-B infusion is associated with infusion-related reactions which comprise of symptoms such as headache, fever, nausea, vomiting, hypotension and thrombophlebitis. This is possibly due to *amphotericin-B-induced cytokine storm with release of tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1)* and this in turn causes fever, chill and hypotension.

Qb. What is the appropriate management of the adverse drug reaction observed in case of CD?

Majority of the infusion-related reactions are mild-to-moderate and the symptoms are generally seen during infusion and subside after the infusion is completed. This effect gradually decreases over a period of 4 to 5 days or tolerance to the effect develops. So, the patient should be counselled regarding this and medication may not be required. If the reactions are intolerable, pretreatment with antipyretic agents (e.g. acetaminophen, NSAIDs or hydrocortisone) may be considered but for short-term use since long-term use of such drugs is associated with negative consequences.

Case Continued

During amphotericin-B therapy CD exhibits renal dysfunction revealed by rise in BUN and creatinine.

Qa. Explain the mechanism responsible for amphotericin-induced renal damage.

The decline in renal function reflected by rise in blood urea nitrogen and creatinine is due to amphotericin-B-mediated vasoconstriction of the afferent arteriole compromising the renal blood flow to the kidney resulting in renal ischemia and damage to renal tubules. This is clinically manifested as azotemia, renal tubular acidosis, hypokalemia and hypomagnesemia.

Qb. What is the reason for anaemia in a patient with renal dysfunction due to amphotericin-B?

As amphotericin-B-induced kidney damage progresses, there is decreased synthesis of erythropoietin which is essential for the formation of red blood cells by the bone marrow. This in turn contributes to anaemia. Both renal and haematologic toxicities are cumulative and dose related.

Qc. What precautions should be taken to prevent renal dysfunction? Will you consider any change in the treatment if CD develops renal dysfunction?

To reduce the risk of nephrotoxicity concurrent use of other nephrotoxic drugs such as aminoglycosides, cyclosporine, etc. should be avoided. Liposomal preparations of amphotericin B has been formulated which are less toxic to the kidney. Fluid management and maintenance of euvolemia is critical to prevent acute kidney injury.

Neprotoxicity might require discontinuation of therapy and switch to alternative less nephrotoxic systemic antifungal drugs (e.g. azoles or echinocandins) may be considered.

Qd. Explain the rationale for combining amphotericin B with flucytosine.

Amphotericin B exhibits synergistic interaction with flucytosine in the treatment of fungal infections. The synergistic interaction is related to the mechanism of action of amphotericin B. Amphoteric B binds to ergosterol, a fungal cell membrane sterol and alters the permeability of fungal cell membrane, facilitating the penetration of flucytosine through the fungal cell membranes. This allows lower dose of amphotericin B to produce therapeutic effect thus minimizing the toxicity associated with amphotericin B.

CASE 4: DRUG THERAPY OF CANDIDA VAGINITIS

A 30-year-old married lady comes to the gynaecology OPD with complains of pruritus, vaginal soreness, dyspareunia, external dysuria and abnormal vaginal discharge. Per speculum examination reveals vulvar edema, fissures, excoriations and thick curdy vaginal discharge. Wet smear of the vaginal discharge demonstrates the presence budding yeasts. A diagnosis of candida vaginitis is made.

Qa. What is the causative organism? Which drugs would you recommend for the treatment of uncomplicated vulvovaginal candidiasis (VVC)?

Vulvovaginal candiasis (VVC) usually is caused by *Candida albicans* but can occasionally be caused by other *Candida* species or yeasts.

Imidazole group of drugs which include *clotrimazole, econazole, and miconazole* are generally used in topical formulations for superficial fungal infections such as candida vaginitis. Short course topical formulations (i.e. single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. Treatment with *azoles* results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy.

Qb. What are the limitations of oral antifungal therapy in the treatment of VVC?

Oral antifungal therapy is associated with greater systemic side effects including nausea, headache and abdominal pain and higher risk of drug interactions than topical antifungal therapy.

Qc. What instructions will you give to the patient who is prescribed clotrimazole vaginal tablet or cream?

The patient is advised to take the drug as prescribed. Compliance is of utmost importance since discontinuing the drug too soon may result in a relapse. The vaginal tablet or cream should be used at bedtime to facilitate retention.

Qd. How will you treat recurrent vulvovaginal candidiasis (VVC)?

Fluconazole is the first choice oral antifungal medicine in a woman who has recurrence of symptoms after treatment of VVC. However, long-term therapy is warranted.

Qe. Can oral antifungal therapy be used in a pregnant woman with VVC?

Oral antifungal medications should not be used by a pregnant women. Topical application of antifungal drugs (miconazole or ketoconazole) may be used. In case of recurrent infections, nystatin may be administered orally and per vaginally thrice daily for 2 weeks.

CASE 5: ANTIFUNGAL THERAPY OF COCCIDIODAL MENINGITIS

A 32-year-old, HIV seropositive male JK, was admitted to the hospital with complaints of severe headache, nausea, vomiting, altered sensorium and blurring vision.
Medical examination

- **Examination of cerebrospinal fluid: Elevated white blood cell count with a mixed or lymphocytic pleocytosis**
- **Serologic examination: Coccidiodal IgG antibody in CSF samples**

Your diagnosis: **Coccidiodal meningitis.**

Qa. How will you manage JK?

- The 2016 guidelines of the Infectious Disease Society of America recommend fluconazole as initial therapy.
- The usual dosage of fluconazole is 400 mg/day. Many physicians begin therapy with 800 to 1200 mg/day of fluconazole.
- If the azole therapy elicits a response, treatment is continued indefinitely because treatment is suppressive rather than curative and relapse rates are high.
- In case of therapeutic failure voriconazole is used for rescue therapy.

Qb. Why is fluconazole the preferred choice in the treatment of coccidiodal meningitis?

The advantages of fluconazole in the treatment of meningitis are as follows:

i. Prior to the advent of azoles, amphotericin B deoxycholate was used which required frequent administration via intrathecal route. The challenge of administration, toxicity associated with this route and lack of experience in utilizing this method, led to the decline of amphotericin B use and made the physicians resort to fluconazole. Fluconazole has improved side effect profile compared to amphotericin B which may be associated with infusion reactions, renal toxicity and hepatotoxicity.

ii. Fluconazole is a hydrophilic triazole that is available in both oral and intravenous formulations. The bioavailability of oral fluconazole is nearly 100% and unlike ketoconazole and itraconazole, its absorption is not influenced by gastric pH.

iii. It has excellent penetration into the cerebrospinal fluid which makes it a suitable drug for the treatment of meningitis.

Qc. What are the limitations of ketoconazole in the management of fungal infections?

Ketoconazole is the prototypic drug of azole class of antifungals. It has largely been replaced as a first-line systemic antifungal medication by other azole antifungal drugs because of the following reasons:

- Ketoconazole requires an acidic environment to become soluble in water and to be absorbed in the gastrointestinal tract. At alkaline pH, it becomes increasingly insoluble thus limiting its absorption. Therefore, antacids, proton pump inhibitors and H2-blockers are avoided in patients receiving ketoconazole.
- It has the potential to cause gynaecomastia and impotence due to decreased androgen synthesis.
- It is a potent inhibitor of hepatic CYP3A enzymes and can cause fatal drug interactions when administered with other drug classes including antiretrovirals, antimicrobials and steroids.

- It demonstrates low penetration into the central nervous system and is not appropriate for the treatment of fungal meningeal diseases.

CASE 6: PHARMACOKINETIC DRUG–DRUG INTERACTION BETWEEN FLUCONAZOLE AND CYCLOSPORINE

A 60-year-old obese male, with a known history of diabetes and hypertension for 25 years, he underwent renal transplant surgery and was on cyclosporine therapy. Six months later, he developed fungal infection of the lungs and treatment was initiated with fluconazole.

Qa. Comment on the possible drug interaction in this patient when treatment is initiated with fluconazole.

Drug–drug interaction is an important consideration whenever an azole is prescribed with multiple drugs. Fluconazole acts by inhibiting 14α-sterol demethylase, a microsomal cytochrome P450 enzyme which destabilises the fungal membrane and ultimately lead to cell death. However, it is not completely selective for fungal P450 enzyme, it may inhibit hepatic P450 enzyme affecting the metabolism of cyclosporine and other drugs which are metabolized by P450 enzymes, thus increasing the risk of toxicity including cyclosporine-related nephrotoxicity and hepatotoxicity. Therefore, patients concomitantly receiving an azole antifungal agent should be treated with lower doses of cyclosporine.

CASE 7: ANTIFUNGAL THERAPY OF INVASIVE ASPERGILLOSIS

A 40-year-old, HIV positive female was admitted to the hospital with history of fever, cough and shortness of breath. He had initially consumed antibiotics but they were not effective and the condition deteriorated over time. He is a known case of diabetes.

Respiratory system examination: Bronchial breath sounds in left supraclavicular and interscapular areas.

Blood test: **Normal white cell count, mildly elevated ESR, other routine blood parameters were normal.**

Sputum test showed *Aspergillus* filaments, culture was positive for *Aspergillus*, chest radiograph revealed a cavity in the upper lobe of the left lung, chest CT scan showed a mass like a fungal ball in the cavity.

Provisional diagnosis/diagnosis: **Invasive aspergillosis.**

Qa. Comment on the drug therapy of invasive aspergillosis. Explain the role of echinocandins in the management of invasive aspergillosis.

The preferred choice of drug for the treatment of invasive aspergillosis is voriconazole. Other therapies include liposomal amphotericin-B and echinocandins (micafungin and caspofungin).

Echinocandins can be used in settings in which azole and polyene antifungals are contraindicated. Favorable attributes of the echinocandin drugs include their excellent side-effect profiles and few drug–drug interactions. However, only parenteral formulations are available for this drug class

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Chapter

20

Antitubercular Drugs

CASE 1: MANAGEMENT OF NEW CASE OF SMEAR POSITIVE DRUG-SENSITIVE PULMONARY TUBERCULOSIS

RX is a 57-year-old male presented to the outpatient department with complaints of fever on and off for 6 weeks duration with productive cough. He had earlier taken a course of antibiotics but there was no improvement.

Sputum microscopic examination is smear positive; chest X-ray shows bilateral infiltrative shadows with a cavitary lesion on the right apical region.

No family history of tuberculosis or history of contact with tuberculosis. There is history of diabetes for more than 20 years and he is a chronic alcoholic. He is also a patient of chronic kidney disease.

Your diagnosis: **New case of smear positive pulmonary tuberculosis.**

Qa. How do you classify the tuberculosis cases for devising drug regimens according to the RNTCP guidelines 2016?

For devising drug regimens, the RNTCP (2016) has classified TB cases into:

1. Drug-sensitive TB: The patient's bacilli are susceptible to all first-line anti-TB drugs (ATDs). All new TB patients who have never taken any ATD or have taken them for less than one month are presumed to have drug-sensitive TB.
2. Multidrug-resistant TB (MDR-TB): The patient's bacilli are resistant to both rifampicin (R) and isoniazid (H) with or without resistance to any number of other first-line drugs.
3. Rifampicin-resistant TB (RR-TB): The patient's bacilli are resistant to R but not to H, with or without resistance to other anti-TB drugs (ATDs). These patients are to be treated as if they have MDR-TB.
4. Mono-resistant TB: The bacilli are resistant to one first-line ATD, but not R-resistant.
5. Poly-drug resistant TB (PDR-TB): The patient's bacilli are resistant to more than one first-line ATD, except both R and H resistance.
6. Extensive drug resistant TB (XDR-TB): A MDR-TB case whose bacilli are additionally resistant to a fluoroquinolone (FQ) and one second-line injectable ATD.

Qb. Enumerate the available drugs for the management of a case of tuberculosis.

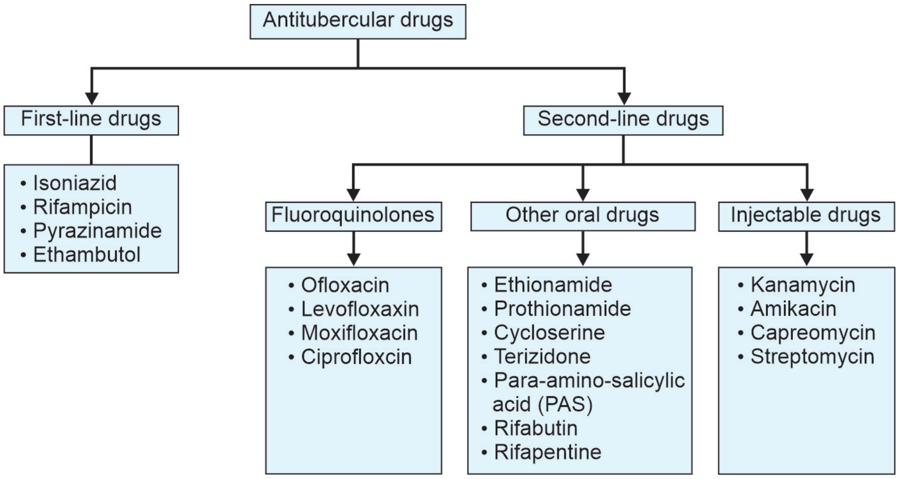
Antitubercular drugs
First-line drugs
• Isoniazid
• Rifampicin
• Pyrazinamide
• Ethambutol
Second-line drugs
Fluoroquinolones
• Ofloxacin
• Levofloxaxin
• Moxifloxacin
• Ciprofloxcin
Other oral drugs
• Ethionamide
• Prothionamide
• Cycloserine
• Terizidone
• Para-amino-salicylic acid (PAS)
• Rifabutin
• Rifapentine
Injectable drugs
• Kanamycin
• Amikacin
• Capreomycin
• Streptomycin

Fig. 20.1: Drugs for tuberculosis treatment

Note: Streptomycin is now considered a second-line TB medicine and is used only as a substitute for amikacin in the following situations: When amikacin is not available, when there is confirmed resistance to amikacin but confirmed susceptibility to streptomycin, and when an all oral regimen cannot be constituted.

Qc. What are the principles of drug therapy for the management of tuberculosis?

The therapeutic strategy for tuberculosis is based on some fundamental principles:

1. Combining different effective drugs to *prevent the selection of resistant mutants* of *M. tuberculosis*, and to cover all groups of tubercular bacilli (rapidly multiplying/slowly multiplying/persisters)
2. Prolonging the treatment to sterilise the infected tissues and therefore *prevent relapse*.

At least *four drugs* likely to be effective compose the regimen, of which *at least two are essential (or 'core' drugs), while two are companion drugs*. The **'core' drugs** are those with the capacity to kill *M. tuberculosis* in any of its metabolic phases. In contrast, the role of the **'companion' drugs** is to support the core drugs, protecting their action and avoiding selection of further resistance.

While one of the core drugs should have a *good bactericidal activity*, the other should have a *good sterilizing activity* and they need to be *maintained for the entire duration of treatment*. While bactericidal drugs efficiently reduce the bulk of the rapidly multiplying bacilli (decreasing infectiousness and avoiding the disease progression), sterilising drugs take care of the population of dormant and semi-dormant bacilli, allowing cure and preventing relapse.

Case Continued

The treatment regimen prescribed for RX was two months of isoniazid, rifampicin, pyrazinamide and ethambutol; four months of isoniazid, rifampicin and ethambutol with a total duration of treatment for 6 months (2 HRZE + 4 HRE).

Qa. Justify the treatment regimen prescribed for RX.

RX is a 'new case of drug-sensitive pulmonary tuberculosis' and therefore the following treatment regimen was prescribed:

i. An initial ***intensive phase (IP)*** with **4 drugs (HRZE)** aimed to rapidly kill the bacilli, bring about sputum conversion and afford fast symptomatic relief.

ii. Intensive phase is followed by a ***continuation phase (CP)*** with **3 drugs (HRE)** during which the remaining bacilli are eliminated so that relapse does not occur.

Principle of treatment of TB has been shifted towards *daily regimen* with administration of daily *fixed dose combination of first-line ATD* as per appropriate weight bands.

The actions of the individual drugs of the antitubercular regimen prescribed for RX are as follows:

- **Isoniazid (H)** *rapidly kills fast multiplying organisms; but only inhibits the quiescent ones.*
- **Rifampicin (R)** acts best on *slowly or intermittently dividing bacilli (spurters).* Both INH and rifampicin are bactericidal and show synergistic action.
- **Pyrazinamide (Z)** acts best on *intracellular bacilli* and those at inflamed sites. It is highly effective during the first 2 months of therapy when inflammatory changes are present. It kills residual intracellular bacilli, has a very good sterilizing activity and reduces treatment duration.
- **Ethambutol** is bacteriostatic, mainly serves to prevent resistance and may hasten sputum conversion.

Qb. Considering that RX is a known case of chronic kidney disease, does his existing antitubercular medications require dose adjustment?

- Isoniazid and rifampicin are eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosage to patients with renal failure.
- Patients with severe renal failure should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.
- Streptomycin, ethambutol and pyrazinamide are however excreted by the kidney. They should be given in reduced doses and renal function be monitored closely.

Case Continued

Two months following the initiation of antitubercular drug therapy, RX presented to the hospital with complaints of paresthesia, numbness, diminished strength in his lower extremities, muscle cramps and difficulty in walking.

Qa. What is the possible reason for the neurological signs and symptoms presented by RX after initiation of antitubercular therapy? Why is INH-related neurotoxicity more common in slow acetylators?

The neurological symptoms such as paresthesia, numbness and weakness could be possibly due to *pyridoxine deficiency* induced by isoniazid (INH). Isoniazid promotes excretion of pyridoxine (vitamin B_6) in urine and inhibits the production of active metabolite pyridoxal phosphate from pyridoxine by inhibiting the kinase enzyme resulting in pyridoxine deficiency.

In slow acetylators (60 to 70% of the Indians) with predisposing conditions such as diabetes, alcoholism, chronic kidney disease, pregnancy, HIV, malnutrition, any other immunocompromised condition, there is increased accumulation of INH with associated pyridoxine deficiency leading to neurotoxicity.

(**Note:** Isoniazid is metabolized primarily by acetylation by liver N-acetyltransferase. The rate of acetylation is genetically determined. In slow acetylators, which contributes to adverse events majority of the Indians (60–70%), adverse events such as peripheral neuritis and hepatotoxicity are common whereas in fast acetylators, there is decreased therapeutic response.)

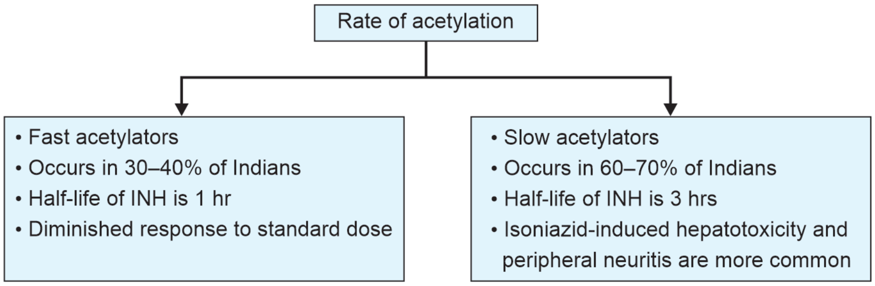
Rate of acetylation
• Fast acetylators
• Occurs in 30–40% of Indians
• Half-life of INH is 1 hr
• Diminished response to standard dose
• Slow acetylators
• Occurs in 60–70% of Indians
• Half-life of INH is 3 hrs
• Isoniazid-induced hepatotoxicity and peripheral neuritis are more common

Fig. 20.2: Fast acetylators *vs* slow acetylators

Qb. How do you prevent the development of INH-related neuropathy while on treatment, particularly in susceptible individuals?

Pyridoxine (vitamin B_6) 20 mg/day should be administered alongside isoniazid to prevent neuropathy in susceptible patients such as malnourished, elderly, pregnant women, HIV infected individuals, diabetic patients, alcoholic and uremic patients. The adverse effects should be closely monitored for such patients. The treatment dose for INH-induced neuropathy is 100 mg per day.

Qc. If RX shows signs and symptoms of hepatitis and blood test results revealed elevated liver enzymes and bilirubin levels, what is the line of action to prevent further liver damage due to antitubercular drugs?

Isoniazid, rifampicin and pyrazinamide are all associated with drug-induced hepatitis. Pyrazinamide is the most hepatotoxic followed by rifampicin. If hepatitis ever occurs, then the physician has the option to substitute pyrazinamide with fluoroquinolone or aminoglycoside.

The only measure available for managing hepatotoxicity is stopping the offending agents, once there is evidence of liver damage and reintroducing the same after normalization of liver enzymes. The order of rechallenge is as follows: start with rifampicin for approximately one week, if no increase in liver fuction test, then add INH for approximately one week, if no increase in LFT then add pyrazinamide and recheck lab tests after approximately one week.

If symptoms recur or LFT show increases in bilirubin > 1.5 and/SGOT or SGPT>5 times the upper normal limit, the last drug added should be stopped and the challenge should continue with the next drug.

CASE 2: DRUG THERAPY OF BONE OR SKELETAL TUBERCULOSIS (DRUG-SENSITIVE EXTRAPULMONARY TUBERCULOSIS)

A 40-year-old male RY attends clinic with presenting symptoms of back pain, weakness in legs. On physical examination, there is spinal tenderness and a palpable mass in the lumbosacral region.

MRI demonstrates involvement of vertebral bodies on either side of the disk and cold abscess.

Molecular-based diagnosis by PCR technique confirms the presence of *M. tuberculosis*. RY is diagnosed with spinal tuberculosis.

Qa. What is the recommended treatment regimen for new case of drug-sensitive extrapulmonary tuberculosis as per Revised National Tuberculosis Control Programme of India, 2016?

Type of TB case	*Treatment regimen (IP)*	*Treatment regimen (CP)*
New case of extrapulmonary tuberculosis (CNS, skeletal and disseminated TB)	(2) HRZE	(4) HRE

Treatment in intensive phase (IP) will consist of 2 months of INH (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in daily dosages as per four weight bands categories.

Only pyrazinamide will be stopped in continuation phase (CP) while the other three drugs will be continued for another 4 months as daily dosages.

As per the guidelines of Revised National Tuberculosis Programme of India, 2016, the *continuation phase (CP) in both new and previously treated cases of extrapulmonary drug-sensitive tuberculosis may be extended 3–6 months* in special situations like tubercular meningitis, bone and joint tuberculosis, spinal tuberculosis with neurological involvement. Extension beyond 3 months will only be on recommendation of experts of concerned field. The total duration of chemotherapy could be for 9 to 12 months.

Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for tubercular meningitis and pericarditis.

CASE 3: DRUG THERAPY OF TUBERCULOUS MENINGITIS

A 20-year-old female PQ, complained dizziness and vomiting for last 10 days, fever for 2 days with headache and neck stiffness. She was delirious with behavioural abnormalities.

CSF examination suggests total white cell count (400 cells/µl), elevated protein levels (300 mg/dl), low glucose (30 mg). CSF mycobacterial culture was positive confirming the diagnosis of tuberculous meningitis.

Treatment: **2 months intensive phase with HRZE followed by 7 months continuation phase with H, R and E.**

Qa. Explain how effectively the antitubercular drugs are delivered to the central nervous system for the management of meningeal tuberculosis, considering the antitubercular drug regimen prescribed in case of PQ.

Blood–brain barrier (BBB) permeation is the main determinant for the effective delivery of drugs to the CNS and is an important factor to be considered in the treatment of meningeal tuberculosis. The penetration capacity of antitubercular drugs through the blood–cerebrospinal fluid/blood–brain barrier for the treatment of central nervous system infections is as mentioned below:

- INH is considered to be the most critical of the first-line agents, due to its excellent CSF penetration and high bactericidal activity.
- Rifampicin penetrates the CSF less freely.
- Pyrazinamide has excellent penetration into the CSF and is a key drug in reducing the total treatment time for drug susceptible TB. Hence, if pyrazinamide cannot be tolerated the treatment course for TBM should be lengthened to a total of 18 months.
- While streptomycin or ethambutol are traditionally used as the fourth antitubercular agent in tubercular meningitis, neither of them penetrates the CSF well in the absence of inflammation and both can produce significant toxicity with long term use.

(**Note:** The newer generation fluoroquinolones, for example, levofloxacin and moxifloxacin have strong affinity against *M. tuberculosis*, excellent CSF penetration and safety profile. Fluoroquinolones are promising agents for the treatment of tubercular meningitis (TBM). However, serum fluoroquinolone concentrations are lowered by concurrent rifampicin use.)

Qb. Do steroids have a role in meningeal tuberculosis? What are the other uses of steroids in tuberculosis patient?

Yes, corticosteroids are commonly used in addition to antitubercular drugs in patients with meningeal tuberculosis. They help reduce inflammation on the surface of the brain and associated blood vessels and are thought to decrease pressure inside the brain and thus reduce the risk of death.

Special situations where steroids are used under adequate chemotherapeutic cover are as follows:

a. In seriously ill patients in order to buy time for drugs to act.
b. Meningeal/renal/pericardial/genitourinary TB or pleural effusion to reduce exudation, prevent its organisation and strictures.
c. In AIDS patients with severe manifestations of tuberculosis.
d. Hypersensitivity reactions to antitubercular drugs.

(**Note:** Corticosteroids are contraindicated in intestinal tuberculosis and may cause silent perforation; if administered should be gradually withdrawn when the general condition of the patient improves.)

CASE 4: DRUG–DRUG INTERACTION OF ANTITUBERCULAR THERAPY AND COMBINED ORAL CONTRACEPTIVES

A 26-year-old lady RZ, diagnosed with sputum smear positive pulmonary tuberculosis became pregnant despite use of combination oral contraceptives (estrogen and progesterone). She was on treatment with isoniazid, rifampicin, pyrazinamide and ethambutol. The lady is curious to know the reason for contraceptive failure.

Qa. Explain the underlying reason for oral contraceptive failure in case of RZ treated with antitubercular drugs.

Cytochrome P450 plays an important role in estradiol metabolism. Combined oral contraceptives contain 35 microgram or less of estrogen. Rifampicin is an inducer of CYP450 enzymes and when coadministered with combined oral contraceptives causes enhanced metabolism of estrogen which is present in low doses, thus reducing the therapeutic efficacy of oral contraceptives. So, the drug–drug interaction between rifampicin and estradiol could be the reason for pregnancy in RZ.

CASE 5: ANTITUBERCULAR DRUG THERAPY IN PREGNANCY

A 28-year-old woman LM, presented to the clinic at 26 weeks of gestation. She reports cough, weight loss, fever, night sweats and one episode of haemoptysis for past one to two months. Her chest X-ray showed right nodular opacity in the apex of the lung field. Further investigations reveal drug-sensitive pulmonary tuberculosis in pregnancy.

Qa. Which antitubercular drugs are safe in pregnancy and may be prescribed in case of LM?

All 4 first-line drugs, ***isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE)*** have an excellent safety record in pregnancy and are not associated with human foetal malformations.

All pregnant women being treated with isoniazid should receive pyridoxine 10–25 mg/day.

Qb. Will you consider any modification in antitubercular therapy of LM during the lactation period? How will you prevent the baby from tuberculosis infection?

All first-line antitubercular drugs are compatible with breastfeeding. Full course of antitubercular therapy should be given to the mother, and breastfeeding should be continued.

The infant should receive 6 months isoniazid preventive treatment after ruling out active tuberculosis followed by BCG vaccination supplemented with pyridoxine 5 mg/day.

CASE 6: MANAGEMENT OF INDIVIDUALS REQUIRING ANTIRETROVIRAL THERAPY AND TB TREATMENT

A 35-year-old HIV patient KY, presented with symptoms of cough, fever, weight loss, and diarrhoea. The patient has been receiving antiretroviral therapy (tenofovir, lamivudine and efavirenz) for past one year.

Investigations: **Sputum microscopy shows sputum smear negative; chest X-ray revealed infiltrates in mid and lower zones of the lung; CD4—T cell count was 400 cells/μl. Line probe assay shows susceptibility to INH and rifampicin.**

Treatment of KY was initiated with isoniazid, rifampicin, pyrazinamide and ethambutol while antiretroviral regimen was continued.

Qa. What are the possible drug-drug interactions between rifampicin and antiretroviral drugs?

Rifampicin stimulates the activity of the hepatic cytochrome P450 enzyme system that metabolizes non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). This mechanism leads to *a reduction in the blood levels of NNRTI and PIs,* and consequently incomplete suppression of HIV replication and the emergence of drug resistance. Rifampicin causes up to 75% reduction in the serum levels of PIs, thus necessitating dosage adjustment.

Rifampicin has *no effect on the serum levels of nucleoside reverse transcriptase inhibitors* (which are not metabolised by cytochromes) and no dose adjustments of these drugs is necessary.

It is to be noted that NNRTIs and PIs can also enhance or inhibit cytochromes and lead to altered blood levels of rifampicin.

Rifabutin, a less potent inducer of cytochrome enzymes may be used as an alternative to rifampicin but for a longer duration (9–12 months) particularly in settings with a limited capacity to adjust dosage of protease inhibitors.

Qb. Is the decision to continue the antiretroviral treatment regimen comprising of tenofovir, lamivudine and efavirenz appropriate for KY? Explain with reasons.

The antiretroviral regimen prescribed for KY is tenofovir, lamivudine and efavirenz and seems to appropriate because of the following reasons:

- In HIV patients, coinfected with tuberculosis and treated with first-line antitubercular agents, *efavirenz is preferred over nevirapine* as a component of ARV regimen. This is because nevirapine is more sensitive to clearance than efavirenz due to the potent enzyme induction activity of rifampicin which leads to subtherapeutic levels of the drug in nevirapine-based regimens.
- Nucleoside reverse transcriptase inhibitors (NRTIs) have less or no potential for drug interactions with rifampicin and hence no dose adjustment is required. This explains the selection of two NRTIs (lamivudine and tenofovir) in case of KY.

CASE 7: DRUG THERAPY FOR MULTIDRUG-RESISTANCE (MDR) TUBERCULOSIS

RT, a 32-year-old female of low socioeconomic background admitted to the hospital after more than 3 weeks of cough, continuous fever, night sweats, malaise and anorexia. She

had earlier taken a course of antibiotics but showed no improvement. Sputum microscopy showed acid-fast bacilli, chest X-ray was non-conclusive. She was suspected as a case of pulmonary tuberculosis and initiated treatment with HRZE for 2 months followed by HRE for 6 months.

After 3 months, she returned to the hospital concerned that she had been coughing up blood for last 2 days. The symptoms such as fever, malaise, nocturnal sweating persisted and there was significant weight loss. A repeat chest X-ray revealed cavity involving the apicoposterior segments of the upper lobe.

The diagnosis is confirmed as multidrug-resistant tuberculosis.

Treatment: **6 months Bdq with Lfx-Cfz-Z-E-Hh-Eto followed by 5 months Lfx-Cfz-Z-E with a total duration of 11 months.**

Qa. How do you define 'multidrug-resistant tuberculosis'?

TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that are resistant to at least both rifampicin and isoniazid.

Qb. Comment on the MDR tuberculosis treatment regimen prescribed for the patient RT.

New shorter, all oral, bedaquiline-containing regimen for eligible MDR-TB patients replaces the standardized shorter regimens with injectables as per the recommendations of WHO. *(WHO guidelines for programmatic management of drug-resistant tuberculosis in India, March, 2021.)*

The regimen lasts for **9–11 months** and the composition of the regimen consists of:

- 4–6 months of bedaquiline (Bdq)–levofloxacin (Lfx)–clofazimine (Cfz)–pyrazinamide (Z)-ethambutol (E)–ethionamide (Eto)–high-dose isoniazid (Hh) followed by
- 5 months of levofloxacin (Lfx)–clofazimine (Cfz)–pyrazinamide (Z)–ethambutol (E)

Qc. Justify the selection of antitubercular drug regimen for RT diagnosed with multidrug-resistant tuberculosis.

For MDR/RR-TB patients without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a shorter, *all oral, bedaquiline-containing regimen*.

In case of RT, the line probe assay suggests resistance to both INH and rifampicin and hence classified as MDR-TB. Fluoroquinolone resistance has been ruled out using drug susceptibity test. There has been no previous exposure to second-line antitubercular agent in case of RT.

Qd. What are the benefits of shorter, all oral, bedaquiline-containing regimen for MDR-TB patients?

The benefits of all oral, bedaquiline-containing regimen for MDR-TB patients are the following:

- Better treatment outcome for patients with MDR/RR-TB by replacing injectable drugs with oral bedaquiline.
- The injectables have well-known toxicities, including irreversible hearing loss, making the treatment more tolerable with improved outcomes.
- Shorter course of treatment with oral bedaquiline-containing regimen.
- Greater compliance to the treatment regimen and a considerable reduction in loss to follow-up in MDR/RR-TB patients.

Qe. Enlist the medicines that are grouped under longer MDR-TB regimens. Mention the duration of longer MDR-TB regimens.

Grouping of medicines recommended for use in longer MDR-TB regimens

Groups and steps	*Medicines*
Group A Include all three medicines	Levofloxacin or moxifloxacin Bedaquiline Linezolid
Group B Add one or both medicines	Clofazimine Clycloserine or terizidone
Group C Add to complete the regimen and when medicines from groups A and B cannot be used	Ethambutol Delamanid Pyrazinamide Imipenem-cilastin or meropenem Amikacin or streptomycin Ethionamide or prothionamide *p*-aminosalicylic acid

In MDR/RR-TB patients on longer regimens, a total treatment duration of ***18–20 months*** is suggested for most patients, the duration may be modified according to the patient's response to therapy.

Qf. List the specific side effects associated with some of the important drugs of MDR-tuberculosis drug regimen.

1. Moxifloxacin, clofazimine and bedaquiline: QT-prolongation effect
2. Linezolid: Neuropathy and myelosuppression
3. Clofazimine: Skin discoloration
4. Cycloserine: Depression and suicidal ideation. Caution should be exercised in pre-existing seizure disorders.
5. Ethionamide: Anorexia, nausea, vomiting, salivation, metallic taste, epigastric discomfort, sulfurous belching and hepatitis, aches and pains, peripheral neuritis, behavioural changes, rashes, impotence, menstrual disturbances and goiter on prolonged use.
6. Pyrazinamide: Hyperuricaemia due to inhibition of uric acid secretion by kidney tubules and gout can occur. Hepatotoxicity is common.
7. Bedaquiline causes nausea, headache, arthralgia and prolongation of QTc interval. Caution is considered in patients using bedaquiline with other QTc prolonging drugs. Bedaquiline has the potential to cause hepatotoxicity.

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Section VII

Special Topics

21. Drugs for Glaucoma
22. Mydriatics and Miotics
23. Drugs for Myasthenia Gravis
24. Drug Therapy for Shock
25. Drugs for Gout
26. Drugs for Rheumatoid Arthritis
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Chapter

21

Drugs for Glaucoma

CASE 1: DRUG THERAPY OF OPEN ANGLE GLAUCOMA

'SK', a 55-year-old male patient underwent routine health check-up. The findings of ophthalmic examination were as given below:

- **Visual acquity without correction is 20/80 and 20/100**
- **Intraocular pressure is 26 mmHg**
- **Ophthalmoscopy revealed physiologic cupping of the optic disc in both eyes**
- **Visual field examination revealed a nerve fibre bundle defect**
- **Gonioscopy showed anterior chamber angles as normal**
- **Pupils were normal in both eyes.**

There is a positive family history of glaucoma. He is a known case of diabetes for 10 years, is on insulin therapy and taking atorvastatin for dyslipidaemia, blood pressure and pulse rate is normal.

SK has a history of bronchial asthma and uses salbutamol inhaler, on an as-needed-basis.

Qa. Given that SK has a history of bronchial asthma, would you consider caution in prescribing β-blocker for the management of glaucoma? If yes, give reasons.

β-blockers may induce severe bronchospasm in susceptible patients due to their antagonistic action on β2-receptors of bronchial smooth muscles inhibiting cyclic adenosine monophosphate (cAMP) production, in turn inhibiting the relaxation of bronchial smooth muscle leading to exacerbation of bronchial asthma.

Qb. If you have to select between timolol and betaxolol eyedrops for SK, which one would you choose? Explain with reasons.

Although betaxolol is somewhat less effective than timolol in lowering intraocular pressure, it is a safer alternative to timolol in bronchial asthma because it is a selective β1-antagonist, having minimal action on β2-receptors which are largely pulmonary. It lowers IOP by inhibiting cyclic adenosine monophosphate (cAMP) production in ciliary epithelium mediated via β1-blocking action. Timolol is a non-selective β1- and β2-antagonist and is more likely to precipitate bronchial asthma due to its antagonistic action on β2-receptors of bronchial smooth muscle.

Qc. Are there any alternative options to beta-blockers that can be used for the treatment of primary open angle glaucoma (POAG)?

The *prostaglandin analogs* are excellent alternatives to beta-blockers for the treatment of POAG because they are at least as effective as the β-blockers, can be administered once a day, and are associated with minimal systemic adverse effects. They increase uveoscleral outflow of aqueous humour and, thereby, decreased IOP.

Carbonic anhydrase inhibitors (CAIs) can also be used for the management of glaucoma. Carbonic anhydrase inhibitors (CAIs) lower IOP by decreasing bicarbonate production and, therefore, the flow of bicarbonate, sodium, and water into the posterior chamber of the eye, resulting in a 40–60% decrease in aqueous humour secretion.

Qd. Considering that SK is a known case of diabetes mellitus and is on insulin therapy, what is the risk associated with the use of β-blockers for the treatment of glaucoma? What precaution needs to be taken?

Patients with diabetes may experience reduced glucose tolerance and masking of hypoglycemic signs and symptoms while on treatment with β-blocker. So, SK is advised to periodically monitor his blood glucose and make necessary adjustments in his medications to avoid the fluctuation in blood glucose level.

Qe. Why is pilocarpine less preferred to β-blocker for the management of intraocular pressure lowering in glaucoma?

- The action of pilocarpine is rapid and short lasting (4–6 hrs) while the effect of β-blockers on aqueous production occurs within 1-hour of instillation and can be present for up to 4 weeks after discontinuation.
- Pilocarpine eyedrops have to be applied more frequently, that is, 6 to 8 hourly instillation is required whereas the β-blocker eyedrops may be applied once or twice daily and this leads to greater convenience and adherence to treatment.
- The fluctuations in intraocular tension are observed more with pilocarpine than β-blocker.
- Pilocarpine action results in contraction of ciliary muscle causing cyclospasm or spasm of accommodation. The patient may experience headache/brow pain or visual blurring when attempting to view objects from a distance (pseudomyopia) and this can be troublesome.
- Beta-blocker does not affect the size of the pupil while pilocarpine produces pupil constriction due to cholinomimetic action on iris sphincter muscle.

Qf. Why is apraclonidine and not clonidine used in the treatment of glaucoma?

Apraclonidine is less lipophilic than clonidine, does not cross the blood–brain barrier as readily, and theoretically has fewer systemic side effects (e.g. hypotension, decreased pulse and dry mouth).

Qg. What are the drugs available for the treatment of glaucoma? Describe the mechanisms through which the drugs act in the management of glaucoma.

Groups	*Drugs*	*Mechanism of action*
Cholinomimetics	Pilocarpine, physostigmine	Pilocarpine, a cholinergic agonist, causes ciliary muscle contraction due to stimulation of M_3 receptors, opens the pores of the canal of Schlemm which facilitates drainage of aqueous humour and reduces intraocular pressure (IOP)

		Physostigmine is an indirect parasympathomimetic agent (indirect agonist of M_3 receptors). The effects of the drug on the eye are similar to pilocarpine
Beta-blockers	Timolol, betaxolol, levobunolol, carteolol	Prevent catecholamine stimulation of β-receptors (β2-subtype) in the ciliary body epithelium and blood vessels, decrease ocular blood flow and aqueous production
Carbonic anhydrase inhibitors	Acetazolamide, dorzolamide	Decrease bicarbonate production by inhibiting carbonic anhydrase enzyme and results in a decrease in aqueous homour secretion
Alpha-agonists	Phenylephrine, apraclonidine, brimonidine	α2-adrenergic receptor agonists, decrease aqueous homour production and increase the uveoscleral outflow
Beta-agonists	Adrenaline, dipivefrine	Increase conductivity of aqueous homour through trabecular meshwork and uveoscleral pathway
Osmotic agents	Mannitol, glycerol	Lower IOP by creating an osmotic gradient between the blood and the ocular fluids
Prostaglandin derivatives and	Latanoprost, bimatoprost	Selective prostaglandin $F_2\alpha$-receptor agonists, increase uveoscleral outflow of aqueous homour decrease IOP

Qh. How does dipivefrine act in glaucoma?

Dipivefrine is a prodrug of epinephrine and is used in the treatment of open angle glaucoma. It penetrates the cornea and is then hydrolysed to epinephrine by esterase enzymes. Epinephrine is an agonist at alpha- and beta-receptors.

It increases outflow of the aqueous humour and also reduces its formation (mediated by its action on α1- and α2-receptors), thus reducing pressure inside the eye. It also increases the conductivity of trabecular filtering cells (β2-receptor-mediated action).

Qi. Why topical dipivefrine is preferred over epinephrine in the treatment of open angle glaucoma?

Dipivefrine is preferred to epinephrine because it is longer acting, more consistent in its action. In terms of side effects, dipivefrine causes minor side effects such as burning, stinging and irritation of the eye. Epinephrine may be associated with serious side effects such as tachycardia, hypertension and arrhythmias. Topical epinephrine should be used with caution in patients with known cardiac history.

CASE 2: USE OF ATROPINE OR PHENYLEPHRINE FOR OPHTHALMOSCOPIC EXAMINATION

A 45-year-old male patient 'JK', experiences poor vision problems. The patient is under treatment for glaucoma. The ophthalmologist wishes to visualise the fundus to rule out abnormalities.

Qa. Which mydriatic would you select for ophthalmoscopic examination in case of 'JK', given that JK has a history of glaucoma, atropine or phenylephrine?

Sympathomimetic agents and anticholinergic drugs are useful for ophthalmoscopic examination. Atropine has antimuscarinic actions on sphincter muscle and ciliary muscle.

This results in pupillary dilation permitting good visualisation of the fundus but the antagonistic action of acetylcholine on M_3-receptors of the ciliary muscle causes relaxation and forward movement of the iris lens diaphragm, which further blocks the drainage channels of the anterior chamber, resulting in *precipitation of angle closure glaucoma.*

Phenylephrine, a sympathomimetic agent produces mydriasis by agonistic action at α1-receptors and subsequent contraction of the radial muscle of iris causing dilatation of the pupil and aids in ophthalmoscopic examination. It is short-acting and safe. There is *no action of phenylephrine on ciliary muscle and intraocular pressure.*

Considering that 'JK' has a history of glaucoma, a sympathomimetic agent such as phenylephrine would be appropriate to dilate the pupil to examine the inner eye. Use of atropine may cause a rise in intraocular pressure and is contraindicated in a patient of glaucoma.

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Chapter

22

Mydriatics and Miotics

CASE 1: USE OF CYCLOPENTOLATE FOR REFRACTIVE ERROR TESTING

A 7-year-old girl 'RY', visited the eye clinic for refractive error testing and was administered cyclopentolate hydrochloride (1%) eyedrops.

Qa. How cyclopentolate eyedrops used in 'RY' is helpful in refractive error testing?

Cyclopentolate antagonizes M_3-receptors of the ciliary muscle of the eye causing its relaxation. As a result, the ciliary muscle cannot contract and change shape of the lens to adjust the focus on near objects. The condition is known as 'paralysis of accommodation' or 'cycloplegia'. The lens is fixed for far vision and near vision is blurred.

A state of cycloplegia is useful in determining the true refractive error of the eye in patients with less than 20/20 vision.

Qb. What are the advantages of cyclopentolate over atropine in refractive error testing?

Characteristics of the ideal cycloplegic agent include rapid onset of action, quick recovery of normal accommodative function, sufficient cycloplegia and no local or systemic side effects.

Cyclopentolate has the following advantages over atropine:

- Cyclopentolate has rapid onset of action which reaches peak effect after 30–45 minutes and the effect washes out after 6–8 hours with complete reversal of cycloplegic effect whereas the cycloplegic action of atropine comes in a few hours (approximately 3 h) and then phases off over in 2–3 weeks.
- Systemic absorption of cyclopentolate is minimal and the risk of serious systemic side effects is less while atropine has the potential to cause systemic side effects which include dryness of mouth and eyes, delirium or restlessness.

Qc. Why do you think atropine is the preferred cycloplegic agent in a child for refractive error testing?

Atropine is the strongest cycloplegic agent and produces complete cycloplegia. It is therefore the preferred cycloplegic agent in young children who have high ciliary muscle tone and require a strong cycloplegic agent.

Qd. Why mydriatics and miotics are used alternatively in keratoconjunctivitis and uveitis?

Mydriatics such as homatropine dilate the pupil and relieve pain by relaxing the ciliary muscle of the iris through their inhibitory action at muscarinic receptors on sphincter pupil and ciliary muscle. Antimuscarinic mydriatics may be alternated with miotics (e.g.

pilocarpine) to prevent adhesions between the iris and the anterior surface of the lens as in keratoconjunctivitis or uveitis.

CASE 2: ATROPINE TOXICITY WITH TOPICAL EYEDROPS

'SK' a boy of 5 years for refraction testing was instructed by the physician to instill atropine eyedrops, one drop in each eye 3 times daily for 3 days. Inadvertently, the mother administered 2 drops in each eye 4 times in a day. On the second day, he developed fever and was restless, disoriented, speech was inappropriate and could not recognize his mother. He could see visual images which others could not see. There was facial flushing, dryness of mouth and urinary retention. The pulse rate was 110 per minute and the pupils were dilated and sluggishly reacting to light.

Qa. How do you explain the constellation of signs and symptoms exhibited by the patient 'SK'?

The signs and symptoms experienced by the patient could be possibly due to atropine toxicity which is a result of systemic absorption via nasolacrimal duct and transconjunctival route. The toxic effects of atropine may be summarized by the saying: 'As blind as a bat, dry as a bone, red as a beetroot and mad as a hatter. Patients are 'blind' owing to the induced cycloplegia, 'dry' due to the inhibition of the sweat and salivary glands (one of the first signs of atropine poisoning is a dry mouth), 'red' because of peripheral vasodilation (produced in an attempt to lose heat and to overcome the lack of function of the sweat glands) and 'mad' owing to effects on the central nervous system (CNS).

Qb. Why physostigmine is preferred to neostigmine in treatment of atropine toxicity?

Physostigmine is a short-acting reversible inhibitor of anticholinesterase, widely used for the treatment of atropine poisoning. It is a tertiary amine alkaloid and hence readily crosses the blood–brain barrier and counteracts *both central and peripheral effects of atropine toxicity*. It increases the concentration of acetylcholine by inhibiting cholinesterase enzyme and enhances acetylcholine signalling at the nicotinic and muscarinic receptors, thus acting as a useful antidote for anticholinergic poisoning.

In contrast, neostigmine is a quarternary ammonium compound and so does not cross the blood–brain barrier, lacks central effects and *only prevents the peripheral effects of atropine toxicity.*

Qc. Mention some of the clinical conditions in which atropine should be used with caution in elderly patients.

1. **Angle-closure glaucoma:** Drugs with antimuscarinic effects can induce acute glaucoma in patients with shallow anterior eye chamber and should be used with caution in patients with glaucoma.
2. **Urinary or GI tract obstruction:** Antimuscarinic agents may reduce the contractility of bladder smooth muscle resulting in acute urinary retention in men with BHP. Reduction of GI motility may also worsen symptoms in patients with intestinal obstruction or ileus.

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Chapter

23

Drugs for Myasthenia Gravis

CASE 1: DRUG THERAPY OF MYASTHENIA GRAVIS

A 32-year-old female RY, arrived at the clinic with complaints of generalised muscle weakness which worsens as the day progresses with increased activity. She is easily exhausted and is unable to perform her duties at workplace efficiently and feels frustrated. Taking rest or having a nap in the middle of the day improves her condition.

She further informs about her ocular symptoms which started one year ago when she experienced blurring vision and noticed drooping of her eyelids towards the evening. She has been finding it difficult to brush her hair or climb stairs and is unable to work at the computer for long time due to eye fatigue.

Over a period of time her muscle weakness has intensified and involved other parts of the body. She is unable to perform her routine activities and feels frustrated. She reports difficulty in swallowing and chewing.

Your diagnosis: **Myasthenia gravis.**

Qa. What is ‘myasthenia gravis’? On what basis have you diagnosed RY as a case of myasthenia gravis?

Myasthenia gravis is an autoimmune neuromuscular disease that leads to weakness and fatigue of skeletal muscle. The smaller muscles responsible for fine movement (i.e. the eye muscles) tend to be affected first, while larger muscles become affected later.

The clinical presentation of RY reveals the following:

- *Eye muscle weakness* indicated by drooping of eyelids or ptosis, blurring vision or diplopia and early eye fatigue making it difficult to work at computer for long periods for RY.
- *Bulbar muscle weakness* which leads to difficulty in speaking, swallowing and chewing.
- *Proximal limb weakness* develops initially which gradually becomes generalised. RY complains of difficulty in brushing hair or climbing staircase, suggestive of weakness in proximal groups of muscles.
- *Respiratory muscle weakness* and failure develops in myasthenic crisis.

On examination, the *deep tendon reflexes are not affected*. There is no impairment of sensations or other neurologic function.

The muscle fatigue worsens throughout the day with increased activity. This is typical in myasthenia gravis.

Qb. Explain the pathophysiology of myasthenia gravis.

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular junction. It is characterized by weakness of skeletal muscles due to damage inflicted to neuromuscular junction by autoantibodies directed against acetylcholine receptors (AchRs) on the postsynaptic membrane.

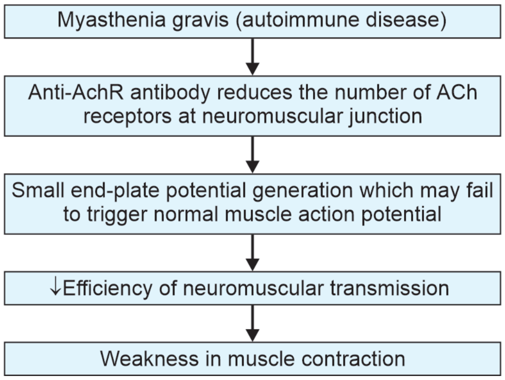
Myasthenia gravis (autoimmune disease)
Anti-AchR antibody reduces the number of ACh receptors at neuromuscular junction
Small end-plate potential generation which may fail to trigger normal muscle action potential
↓Efficiency of neuromuscular transmission
Weakness in muscle contraction

Fig. 23.1: Pathophysiology of myasthenia gravis

Qc. What is the therapeutic objective in the management of myasthenia gravis?

The therapeutic objective in myasthenia gravis is:

- To maximize the activity of acetylcholine at the remaining receptors in neuromuscular junction and
- To minimise or abolish the immunological attack on motor end-plates.

Qd. What are the available treatment options in the management of myasthenia gravis?

1. **Acetylcholinesterase inhibitors** (pyridostigmine and neostigmine) are first-line drugs in myasthenia gravis for symptomatic relief.
2. **Supplemental immunosuppressants:** If symptoms persist despite anticholinesterase treatment. These are:
    - Glucocoticoids
    - Alternatives: Azathioprine, cyclosporine, mycophenolate mofetil
3. **Rapid immunomodulating therapy:** In cases of myasthenic crisis:
    - Plasmapheresis
    - IV immunoglobulins
4. **Thymectomy**

Case Continued

RY was prescribed oral pyridostigmine at a dose of 60 mg every 6 hours and prednisone 10 mg/day. The prednisone was increased by 10 mg every 5 to 7 days to a peak dose of 60 mg.

Qa. How does pyridostigmine act and why is pyridostigmine preferred over physostigmine in the treatment of myasthenia gravis?

Pyridostigmine, a synthetic acetylcholinesterase inhibitor, blocks the hydrolysis of the acetylcholine neurotransmitter in the synaptic cleft. This raises the concentration of acetylcholine and increases the number of interactions between the acetylcholine and the acetylcholine receptor in the neuromuscular junction.

Pyridostigmine is a quarternary compound, does not cross the blood–brain barrier, thereby limiting central nervous system toxicity unlike physostigmine which is a tertiary compound and can readily cross the blood–brain barrier giving rise to CNS side effects. Therefore, pyridostigmine is preferred over physostigmine in the treatment of myasthenia gravis.

Case Continued

RY self-administered higher doses of pyridostigmine for greater therapeutic effect but it resulted in further worsening of symptoms of muscle weakness, dyspnea, sweating, disorientation, and urinary and faecal urgency.

She was admitted to the hospital and diagnosed with 'cholinergic crisis' due to excessive intake of pyridostigmine.

Qa. What is 'cholinergic crisis'? How is it different from 'myasthenic crisis'?

Cholinergic crisis is due to excessive cholinergic activity. Higher doses of cholinesterase inhibitors increase the concentration of acetylcholine at the nicotinic receptors of the neuromuscular junction leading to excessive action of acetylcholine at the muscle end-plate producing flaccid muscle paralysis that is clinically indistinguishable from weakness due to myasthenia gravis. In contrast, *myasthenic crisis* is due to insufficient medication or drug resistance.

Qb. How would you differentiate clinically myasthenic crisis from cholinergic crisis?

Clinical features	*Myasthenic crisis*	*Cholinergic crisis*
Pupil	Normal	Miosis
Fasciculations	None	Present
Heart rate	Tachycardia	Bradycardia
Skin	Cold and faint	Warm and flushed
Bronchial secretions	Normal	Increased

Qc. Which test is used to distinguish cholinergic crisis from myasthenic crisis?

Anticholinesterase test (Tensilon test) is used to differentiate myasthenic crisis from cholinergic crisis. Edrophonium inhibits acetylcholinesterase (AchE) enzymes and allows acetylcholine to interact with limited number of acetylcholine receptors repeatedly producing improvement in strength of myasthenic muscle.

If an initial dose of 2 mg edrophonium is given intravenously, it causes an improvement in muscle power, the test is positive. This improvement occurs within 20 seconds and lasts for 2–3 minutes. Positive test indicates myasthenic crisis. If there is no improvement or further worsening of muscle weakness it indicates cholinergic crisis.

Qd. Why is edrophonium selected among the various anticholinesterases available for differentiating myasthenic crisis from cholinergic crisis?

Cholinesterase inhibitors such as neostigmine and pyridostigmine have a prolonged action at the neuromuscular junction and in cholinergic crisis, where a person has too much of neuromuscular stimulation, these drugs will make the muscle weakness worse by inducing a depolarizing block and since the recovery of drug effect takes time it can result in serious complications. In contrast, *edrophonium acts rapidly, has a brief duration of action, about 10 to 30 minutes and the recovery of the drug effect is quick,* so it is a suitable drug for differentiating myasthenic crisis from cholinergic crisis without having negative consequences of excessive cholinergic stimulation in case of cholinergic crisis.

Qe. What are the potential long-term complications of steroids when used in the management of myasthenia gravis? If steroids pose problems for the patient RY, what alternative drug therapy can be used?

Although corticosteroids are considered as most effective oral immunosuppressive agents and widely used as first-line agent in patients with myasthenia gravis, its side effects pose significant challenges in its clinical use. The systemic side effects of long-term corticosteroid therapy are numerous and include weight gain, diabetes, hypertension, eye disease (cataract and glaucoma), accelerated bone demineralisation and neuropsychiatric disturbances. Potential complications should be discussed before the initiation of treatment and monitored closely.

Immunosuppressive drugs such as azathioprine, cyclosporine, mycophenolate mofetil can be used if there are side effects.

Qf. One year later, RY plans to become pregnant and is curious to know about the potential implications of drug therapy in pregnancy. What would you tell her? How safe are the drugs used for myasthenia gravis in pregnancy?

Anticholinesterase inhibitors have been safely used in pregnant patients with myasthenia gravis and in 50% of the patients monotherapy is sufficient.

Corticosteroid therapy appears to be safe during pregnancy with little teratogenic risk. Only a slight increase in the incidence of cleft palate has been described.

Azathioprine is not recommended in pregnancy as fetuses exposed have an increased risk of myelosuppression.

Cyclosporine A is not necessarily associated with severe effects to the fetus, although fetal myelosuppression, prematurity and spontaneous abortion have been observed. Mycophenolate mofetil, methotrexate and cyclophosphamide are contraindicated in pregnancy.

Plasmapheresis has been safely accomplished throughout pregnancy, especially when a short-term benefit is needed.

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Chapter

24

Drug Therapy for Shock

CASE 1: DRUG THERAPY OF HYPOVOLAEMIC SHOCK

A 45-year-old male patient RX, was brought to the casuality in disoriented state with severe injuries and major blood loss, following road traffic accident. The patient presented with acute dyspnea, cough and abdominal pain. On examination, blood pressure was 80/40 mm of Hg and pulse rate 135/minute, respiratory rate 35 breaths per min and with cold extremities.

On monitoring, the haemodynamic profile shows low central venous pressure (CVP), low pulmonary capillary wedge pressure (PCWP), low cardiac output (CO) and cardiac index (CI) and high systemic vascular resistance (SVR).

Qa. In patient RX, classify the 'type of shock' on the basis of clinical features and haemodynamic profile.

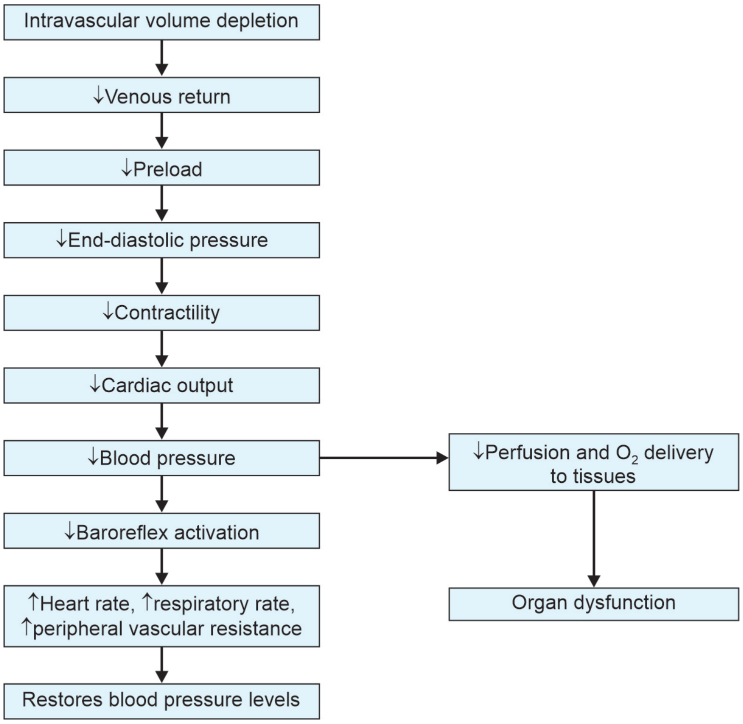

Intravascular volume depletion
↓Venous return
↓Preload
↓End-diastolic pressure
↓Contractility
↓Cardiac output
↓Blood pressure
↓Perfusion and O₂ delivery to tissues
Organ dysfunction
↓Baroreflex activation
↑Heart rate, ↑respiratory rate, ↑peripheral vascular resistance
Restores blood pressure levels

Fig. 24.1: Haemodynamic effects of hypovolaemic shock

Clinical history reveals road traffic accident with traumatic injury to the abdomen with associated blood loss and clinical findings as the following:

- The extremities are cold and there is altered sensorium due to decreased perfusion to the extremities and to the brain.
- The mean arterial pressure has fallen to 52 mmHg due to intravascular volume depletion. This activates the hypothalamic–pituitary–adrenal axis and autonomic nervous system to release catecholamines (epinephrine, norepinephrine). The subsequent increase in heart rate, i.e. 135/min and contractility helps maintain cardiac output.
- The peripheral vasoconstriction caused by the sympathomimetic response helps maintain arterial pressure. The peripheral stimulation of pulmonary J-receptors and carotid body chemoreceptors as well as hypoperfusion of medullary respiratory centre results in high respiratory rate, i.e. 35 breaths/min.

Haemodynamic monitoring indicates loss in circulatory volume, decreased venous return, decreased filling of the cardiac chambers (↓ preload) and hence a decreased cardiac output. The increased systemic vascular resistance is due to increased sympathetic and renin–angiotensin–aldosterone system (RAAS) activation.

Haemodynamic findings (hypovolaemic shock)	
Heart rate	↑
Blood pressure	↓
Cardiac output	↓
Preload (PCWP)	↓
Afterload (SVR)	↑

Therefore, based on the above-mentioned findings, the case is classified under ‘haemorrhagic shock’.

Case Continued

Warmed LR (Ringers’s lactated) solution (2 L) was infused rapidly and the SBP increased to 92 mmHg, but the bleeding has not stopped. LR is continued, to maintain hemodynamic stability while waiting for fully cross-matched blood.

Qa. What is the goal of volume replacement in hypovolemic shock?

Loss of circulating fluid decreases venous return, decreased end-diastolic pressure and decreased force of contraction. The reduced myocardial contractility decreases the cardiac output and results in hypotension and poor perfusion.

The immediate goal is restoration of effective perfusion and oxygen delivery to vital organs and tissues before the onset of cellular injury. This in turn primarily depends on mean arterial pressure (MAP) and cardiac index (CI).

The following parameters are monitored to determine the success of fluid resuscitation:

- MAP >60–65 mmHg
- CI >3.0 to 3.5 L/min/m^2
- Arterial saturation >92%
- Normalization of serum lactate (to <2.2 meq/L)
- Maintain urine output >0.5 ml/kg/hr

Qb. What are the options available for fluid resuscitation in the management of hypovolemic shock?

The therapeutic goal in hypovolaemic shock is expansion of intravascular volume by fluids which include crystalloids, colloids or blood products.

Resuscitative crystalloids are isotonic solutions that include either saline (0.9% sodium chloride; 'normal saline' [NS]) or a saline equivalent (lactated Ringer's [LR] solution) .

Colloidal solutions contain high molecular weight molecules that are derived from natural products, such as proteins (albumin), carbohydrates (dextrans, starches), and animal collagen (gelatin).

Blood and blood substitutes are indicated for augmenting oxygen carrying capacity and not for volume expansion.

Qc. Why do you think crystalloids are preferred over colloids for fluid resuscitation in haemorrhagic shock as in case of RX? Explain with reasons.

The Cochrane Report (Alderson, et al. 2001) states that there is no evidence to indicate that colloids improve mortality in the critically ill patients. Given, the outcome of crystalloid and colloids in terms of mortality, is similar. The increased availability of crystalloids, their decreased cost and fewer adverse reactions, makes crystalloids the preferred choice in hypovolemic shock.

Synthetic colloids are associated with major side effects which are the following:

- Allergic reactions (including anaphylaxis)
- Coagulation abnormalities due to hemodilution thus diluting the coagulation factors and favouring increased bleeding due to weakening of clot formation.
- Renal failure as with hydroxy ethyl starch that has been reported to increase mortality and increase risk of acute kidney injury.

Excessive use of colloids can precipitate cardiac failure, pulmonary and peripheral edema. This can result in small increase in the risk of death.

Case Continued

Following fluid replacement, 'vasopressor' agent was needed to maintain adequate ventricular performance and achieve haemodynamic stability.

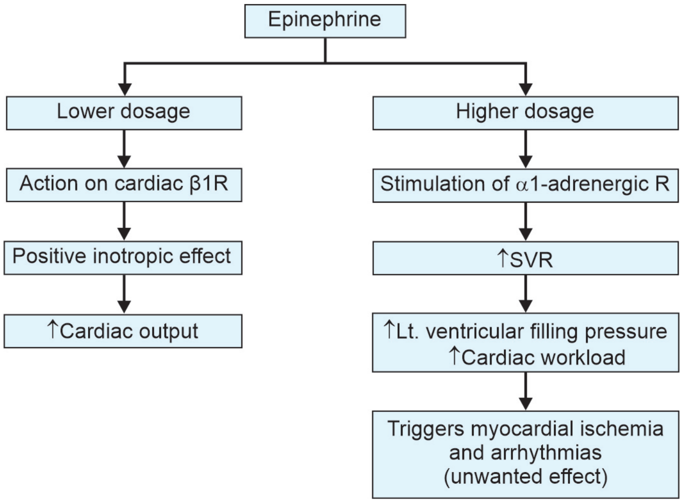
Qa. What is meant by 'vasopressor' agent? Mention the vasopressor agents that are available for the management of shock.

A 'vasopressor' agent refers to any substance that raises blood pressure. These agents are categorized into:

i. **Ionotropic/chronotropic agents (increase cardiac contractility and cardiac output):** Dobutamine
ii. **Vasoconstrictor agents (increase systemic vascular resistance and raise blood pressure):** Phenylephrine, vasopressin
iii. **Mixed pressor agents (act through both mechanisms):** Epinephrine, norepinephrine and dopamine

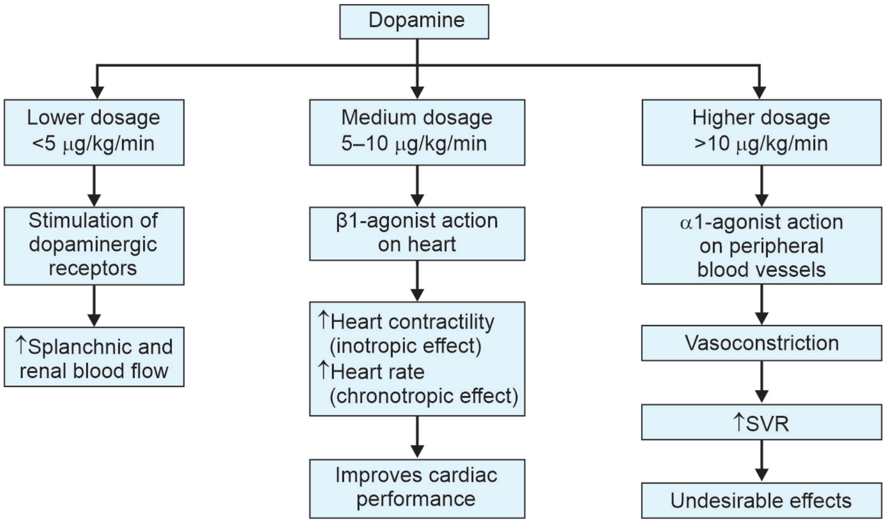
Qb. Mention any TWO vasopressors that can be initiated in the management of hypovolemic shock. How 'dosage' of these drugs influence receptor selectivity and pharmacological actions?

Dopamine and epinephrine are commonly used vasopressor agents in the management of hypovolemic shock.


Epinephrine
Lower dosage
Action on cardiac β1R
Positive inotropic effect
↑Cardiac output
Higher dosage
Stimulation of α1-adrenergic R
↑SVR
↑Lt. ventricular filling pressure
↑Cardiac workload
Triggers myocardial ischemia and arrhythmias (unwanted effect)

R: Receptor; SVR: Systemic vascular resistance

Fig. 24.2: Haemodynamic effects of epinephrine in shock


Dopamine
Lower dosage <5 μg/kg/min
Stimulation of dopaminergic receptors
↑Splanchnic and renal blood flow
Medium dosage 5–10 μg/kg/min
β1-agonist action on heart
↑Heart contractility (inotropic effect)
↑Heart rate (chronotropic effect)
Improves cardiac performance
Higher dosage >10 μg/kg/min
α1-agonist action on peripheral blood vessels
Vasoconstriction
↑SVR
Undesirable effects

SVR: Systemic vascular resistance

Fig. 24.3: Haemodynamic effects of dopamine in shock

Dopamine is a mixed pressor agent, acts on α, β and dopaminergic receptors depending on ***dosage*** administered. The beneficial effects of dopamine in management of shock are seen at *lower and medium* dosage. At lower dosage (<5 μg/kg/min), *dopaminergic* receptors of the renal and splanchnic blood vessels are stimulated increasing the renal blood flow and perfusion to the kidney. At medium dosage (5–10 μg/kg/min) *beta-mediated* inotropic effect is seen.

Epinephrine is a potent mixed α- and β- adrenergic agonist and *acts as an inotrope due to its primary action on beta-receptors at lower dosage.*

Both dopamine and epinephrine at **higher dosages have predominant effect on α1-adrenergic** receptors causing vasoconstriction which is undesirable in low cardiac output states in which the systemic vascular resistance is already high. Further, increased afterload due to high resistance in peripheral vasculature increases cardiac oxygen demand which may trigger myocardial ischaemia and arrhythmias. Therefore, high dosages of dopamine and epinephrine are avoided in the management of shock.

Qc. What are the drawbacks of epinephrine as a vasopressor agent in hypovolemic shock?

Epinephrine induces hypermetabolism and glycolysis resulting in lactic acidosis and hyperglycaemia. Increased lactic acid production contributes to metabolic acidosis which participates in the reduction of cardiac contractility and in the vascular hyporesponsiveness to vasopressors through various mechanisms leading to deleterious effects.

CASE 2: DRUG THERAPY OF CARDIOGENIC SHOCK

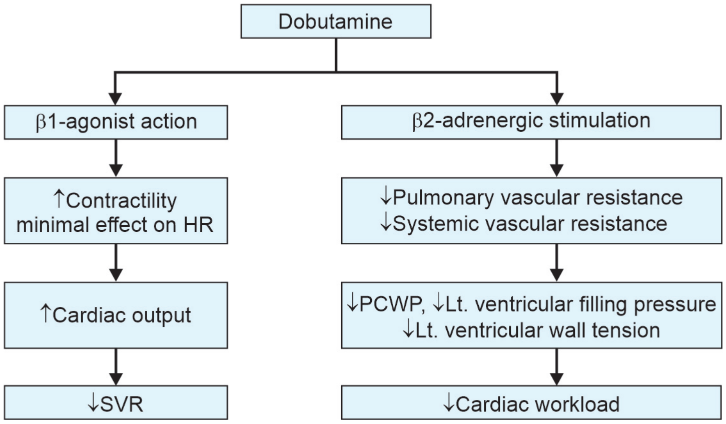
A 55-year-old male patient was admitted to the emergency department with complaints of acute chest pain, sweating and shortness of breath. In his case records, you come across history of ischemic heart disease.

On examination, **skin is cold, there is altered levels of consciousness, blood pressure is 88/56 mmHg, heart rate 110 beats/min.**

Haemodynamic profile: **PCWP (mmHg) = 26–30 mmHg, cardiac index = 1.6 L/min/m^2, left ventricular ejection fraction is 30%.**

Haemodynamic findings in cardiogenic shock	
Heart rate	↑
Blood pressure	↓
Cardiac output	↓
Preload (PCWP)	↑
Afterload (SVR)	↑

Qa. Mention the first choice vasopressor for the treatment of cardiogenic shock with heart failure. Explain the rationale for its use.


Dobutamine
β1-agonist action
β2-adrenergic stimulation
↑Contractility
minimal effect on HR
↓Pulmonary vascular resistance
↓Systemic vascular resistance
↑Cardiac output
↓PCWP, ↓Lt. ventricular filling pressure
↓Lt. ventricular wall tension
↓SVR
↓Cardiac workload

SVR: Systemic vascular resistance; PCWP: Pulmonary capillary wedge pressure

Fig. 24.4: Actions of dobutamine in cardiogenic shock

Dobutamine is the drug of choice for the treatment of cardiogenic shock with heart failure. Cardiogenic shock as a result of poor left ventricular pump function is characterized by high PCWP, low CO and CI, and generally a high SVR.

Dobutamine has predominant action on β-receptors (β1- and β2-receptors).The β1-receptor-mediated positive inotropic action and β2-receptor-mediated vasodilatory action increase cardiac output and decrease systemic and pulmonary vascular resistance with improvement in diastolic coronary blood flow. It also prevents increase in infarct size in patients with acute myocardial infarction by improved collateral blood flow and balances between oxygen supply and demand.

Therefore, dobutamine is the preferred vasoactive agent to treat cardiogenic shock with heart failure. However, caution should be observed if administered to hypotensive patients, especially with coexistent hypovolemia because of β2-mediated vasodilation.

Qb. Which drug other than dobutamine has inotropic action and causes vasodilation that is useful in cardiogenic shock?

Milrinone lactate, a selective phosphodiesterase III inhibitor, prevents degradation of cyclic AMP and acts as an inodilator. It increases ionotropy and decreases systemic vascular resistance via cyclic adenosine monophosphate.

Qc. Mention the vasodilators that are useful in acute ventricular failure with cardiogenic shock.

For ***preload reduction*** nitroglycerine is the agent of choice and for ***afterload reduction***, sodium nitroprusside, hydralazine hydrochloride, angiotensin-converting enzyme inhibitors and fenoldopam are preferable.

CASE 3: DRUG THERAPY OF SEPTIC SHOCK

A 75-year-old man SK, arrived in the emergency department with severe abdominal pain. He is confused and drowsy. On examination, the systemic arterial blood pressure was 80/55 mmHg, heart rate was 120 beats per minute and RR 28/min. The extremities are cold and cyanosed. There is history of diabetes mellitus and hypertension.

The abdomen was tense and distended. CT scan is suggestive of intestinal perforation. Surgery was performed with peritoneal toilet and wash out. He was diagnosed with septic shock.

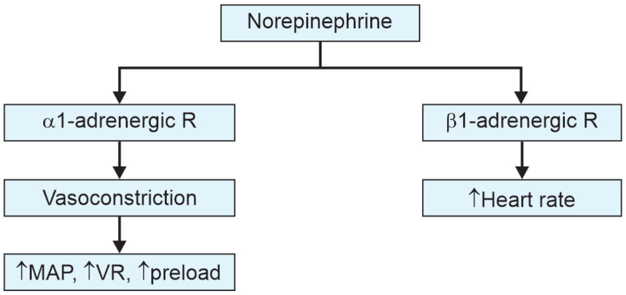
In the operating room, he received 3–4 L of crystalloids. The arterial blood pressure is supported with a norepinephrine infusion. He was treated with intravenous antibiotics.

Haemodynamic findings in septic shock	
Heart rate	↑
Blood pressure	↓
Cardiac output	↑ Early in septic shock but ↓ in severe shock
Preload (PCWP)	–
Afterload (SVR)	↑

Qa. Compare the pharmacological actions of norepinephrine and dopamine in the management of septic shock. Why norepinephrine is preferred over dopamine in septic shock?

Septic shock is a life-threatening illness characterized by poor vascular tone in the peripheral circulation, hypotension, impaired organ function and/or failure, and metabolic abnormalities. To maintain adequate organ perfusion, the administration of vasopressor is required. *Norepinephrine and dopamine* are the most commonly used vasopressors for septic shock in patients who do not respond to fluid resuscitation.

Norepinephrine has marked *vasoconstrictive characteristics due to predominant action on α1-receptors* resulting in increased mean arterial pressure (MAP), effective circulating blood volume, venous return and preload and effectively reverses the hypotension in vasodilatory shock. It also has *weaker action on β1-adrenoceptors* but its action on beta1-receptors is cancelled out by a reflex bradycardia in response to the increased blood pressure. Therefore, overall, the heart rate remains unchanged leading to lesser incidence of tachycardia or tachyarrhythmias. Unlike epinephrine, norepinephrine has *no action on β2-receptors* which mediates vasodilation and this is an additional advantage for its use in septic shock which is vasodilatory in nature.



MAP: Mean arterial pressure; VR: Venous return

Fig. 24.5: Actions of norepinephrine in septic shock

Dopamine is often effective for restoring mean arterial pressure in patients with septic shock. At *medium dosages, dopamine exerts inotropic action due to stimulation of beta1-adrenoceptors* which is primarily responsible for improving the blood pressure. However, dopamine is associated tachycardia and at higher dosage vasoconstriction, which can lead to increased cardiac oxygen demand and decreased oxygen delivery and may trigger myocardial ischaemia and arrhythmias.

Therefore, noradrenaline might be preferred over dopamine as the first-line vasopressor to avoid cardiovascular events.

Qb. In which clinical situation is phenylephrine preferred over norepinephrine in the treatment of septic shock and why?

Phenylephrine is preferred over norepinephrine and dopamine in the management of septic shock in patients with tachycardia and who are at increased risk for arrhythmias. It *has pure alpha-adrenergic activity with virtually no affinity for beta-adrenergic receptors.* Due to agonistic action on alpha-receptors, there is vasoconstriction, raised peripheral vascular resistance and restoration of mean arterial pressure in septic shock. There is minimal risk of tachycardia due to absence of beta1-stimulation with phenylephrine in contrast to dopamine or norepinephrine which causes tachycardia as a side effect. Therefore, phenylephrine is preferred over norepinephrine and dopamine in the management of septic shock in patients with tachycardia.

Qc. Describe the antibiotic therapy in septic shock.

Evaluate the source of sepsis. The selection of appropriate antibiotics should be based on sound clinical judgement plus knowledge of the antimicrobials used.

Antibiotics must be broad spectrum agents and must cover gram-positive, gram-negative and anaerobic bacteria because organisms from any of these different classes can produce the same clinical picture as distributive shock.

- For immunocompetent patients, monotherapy is usually adequate with carbapenems (e.g. imipenem and meropenem), 3rd or 4th generation cephalosporins (e.g. cefotaxime, ceftriaxone, cefepime, cefoperazone, ceftazidime) or extended-spectrum penicillin (e.g. ticarcillin and piperacillin).
- Immunocompromised patients or at high risk for multidrug-resistant organisms, typically require dual broad spectrum antibiotics.
- In patients with history of IV drug use, those with indwelling vascular catheters or devices, or those with recent hospitalizations, the increasing prevalence of MRSA must be taken into account, and an agent such as vancomycin or linezolid should be included.
- Antianaerobic coverage is indicated in patients with intra-abdominal or perineal infections.

After culture results are known, the antibiotic regimen should be narrowed to cover the specific infecting microorganism using the least expensive and least toxic antibiotic available.

Qd. Do corticosteroids have a role in the management of septic shock? Explain with reasons.

The guidelines of the surviving sepsis campaign recommend treatment with 200 mg of hydrocortisone per day, if adequate fluid resuscitation and treatment with vasopressor agents do not restore hemodynamic stability. However, the guidelines stipulate that glucocorticoids should not be administered for the treatment of sepsis in the absence of shock.

Hydrocortisone therapy suppresses the formation of prostaglandins and shorten the duration of use of vasopressors besides reducing mortality. Moderate doses of corticosteroids are useful in the management of patients with early severe ARDS, a complication of septic shock.

CASE 4: DRUG THERAPY OF ANAPHYLACTIC SHOCK

A 52-year-old female patient RX, suddenly developed generalized urticaria with pruritus, abdominal cramps, vomiting, tongue swelling and difficulty in breathing after the nurse injected 300,000 units of penicillin G in aqueous suspension in the gluteal region for asthmatic bronchitis. The patient was in acute distress and confused. On examination, the vital signs are: (a) Blood pressure: 65/54 mmHg; (b) respiratory rate: 34 breaths/min; (c) hart rate: 124 beats/min.

On inspection of the body, urticaria of palms, soles and inner thighs are noticed. Chest auscultation reveals diffuse wheezes, bilaterally.

Acute anaphylactic reaction was suspected in RX and epinephrine was administered intramuscularly in the anterolateral thigh at a dosage of 0.3–0.5 mg of a 1:1000 w/v solution.

Qa. What is ‘anaphylaxis’? Mention the common causes that can lead to anaphylaxis. Identify the probable cause of anaphylactic shock in case of RX.

Anaphylaxis is systemic, immediate hypersensitivity reaction, caused by IgE-mediated release of mediators from mast cells, basophils and recruited inflammatory cells.

Anaphylaxis is defined by a number of signs and symptoms, alone or in combination, which occur within minutes, or up to a few hours, after exposure to a provoking agent.

Anaphylaxis can be commonly caused by any of the following agents:

- Antibiotics: Penicillin, cephalosporins, sulfamethoxazole
- Proteins: Venoms, latex, seminal fluid, hormones such as ACTH, insulin, PTH, GnRH, enzymes as streptokinase.
- Foods: Peanuts, crustaceans, fish, milk, egg, soy and many others
- Intravenous contrast used in imaging tests.

The possible cause of anaphylaxis in RX is penicillin administration which is the most common cause of anaphylaxis. Penicillin and other antibiotics are haptens, molecules that are too small to elicit immune responses but they may bind to serum proteins and produce IgE antibodies.

Qb. Describe the clinical features of anaphylactic shock.

Anaphylaxis is a systemic event and in vast majority of subjects two or more systems are involved.

Gastrointestinal: Symptoms include nausea, vomiting, diarrhea, and abdominal pain. These symptoms are likely due to intestinal smooth muscle contraction and alterations in water and electrolyte absorption.

Mucocutaneous symptoms (e.g. flushing, pruritus, angioedema, and urticaria) are common in anaphylaxis.

Respiratory: Upper airway symptoms develop due to fluid extravasation causing mucosal edema and obstruction. Some symptoms of upper airway involvement include angioedema, stridor, dysphagia, and rhinorrhea. Lower airway obstruction involves bronchospasm and wheezing.

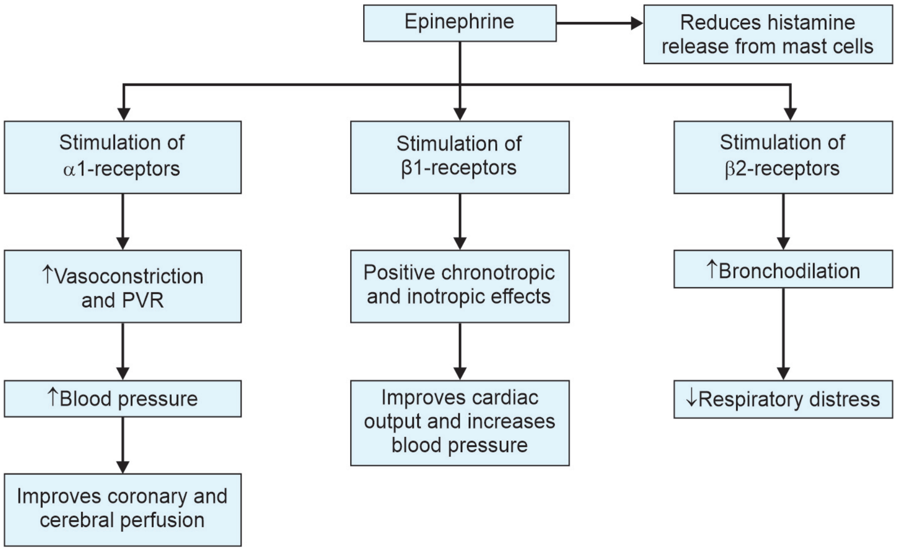
Cardiovascular: Signs and symptoms develop due to direct and indirect effects of mediators on the vasculature and heart. Increased vascular permeability causes rapid fluid extravasation and vascular smooth muscle relaxation causing vasodilation and a rapid decrease in systemic vascular resistance with symptoms of faintness, hypotension, hypovolemic shock and arrhythmias.

Neurologic changes are mostly secondary to hypotension and decreased perfusion and manifest as dizziness, confusion, syncope/presyncope, or headache.

Qc. Mention the signs and symptoms that are consistent with the diagnosis of anaphylactic shock in patient RX.

The patient ‘RX’ presents with signs and symptoms which favour the diagnosis of anaphylactic shock. There are signs and symptoms of generalized mediator release such as urticaria, pruritus, flushing and angioedema. Hypotension has been documented and the patient is in hypovolemic shock. There is airway obstruction such as glossal edema and severe bronchospasm.

Qd. Explain why epinephrine is the preferred medication in anaphylactic shock.


Epinephrine
Reduces histamine release from mast cells
Stimulation of α1-receptors
Stimulation of β1-receptors
Stimulation of β2-receptors
↑Vasoconstriction and PVR
Positive chronotropic and inotropic effects
↑Bronchodilation
↑Blood pressure
Improves cardiac output and increases blood pressure
↓Respiratory distress
Improves coronary and cerebral perfusion

PVR: Peripheral vascular resistance

Fig. 24.6: Actions of epinephrine in anaphylactic shock

Epinephrine is the drug of choice for anaphylaxis. It produces beneficial effects by stimulating both alpha- and beta-adrenergic receptors. The agonistic action of epinephrine on α1-receptors increases blood pressure by peripheral vasoconstriction. The positive inotropic and chronotropic action of β1-receptor stimulation, raises blood pressure and improves coronary and cerebral perfusion. The β2-stimulatory action on receptors induces bronchodilation and relieves respiratory distress. The increased cyclic AMP levels inhibit mediator release from mast cells and basophils.

Animal and human data indicate that platelet-activating factor (PAF) mediates life-threatening manifestations of anaphylaxis. The early use of epinephrine *in vitro* inhibits the release of PAF in a time-dependent manner, giving support to the use of this medication with the first signs and symptoms of anaphylaxis.

Qe. Compare the use of norepinephrine and epinephrine in the treatment of anaphylactic shock.

Norepinephrine is an adrenergic agonist similar to epinephrine, but unlike epinephrine it has no β2-action and does not relieve bronchospasm associated with anaphylactic shock. Therefore, epinephrine has an advantage over norepinephrine in the treatment of anaphylactic shock and is the drug of choice.

Qf. Do you think beta2-agonists would be useful in the treatment of acute anaphylactic shock? Comment on the therapy.

Nebulized albuterol or other beta2-agonists may be useful to treat respiratory distress which is due to bronchoconstriction but would be ineffective in restoring the blood pressure to normal because of absence of α1-action and presence of β2-agonistic action on vasculature which would cause vasodilation and further fall in blood pressure. There is no clinical trial on use of these medications in anaphylaxis and their effectiveness in treating other allergic diseases offers some basis for their use.

Qg. Given that the route used for administration of epinephrine is intramuscular, what do you think is the risk if adrenaline is administered intravenously? What is the drawback of subcutaneous route of epinephrine administration in a state of shock?

If the patient is refractory to treatment with epinephrine administered intramuscularly, 100 µg epinephrine is administered intravenously over 5–10 min. Intravenous route increases the risk of cardiovascular reactions. Epinephrine is stopped immediately if there is chest pain or evidence of arrhythmias. Therefore, intravascular route is used with caution.

In anaphylactic shock, the blood flow to the skin and mucosal tissues is reduced. This delays the absorption of the drug via subcutaneous route. Hence, subcutaneous route is not commonly used when the patient is in shock.

Qh. Glucocorticoids are not preferred in the initial treatment of acute anaphylaxis despite their potent anti-inflammatory effect. Why?

Although glucocorticoids are potent anti-inflammatory agents and are highly effective in reactive airway disease, they are not preferred in the initial treatment of acute anaphylaxis because the onset of action is delayed for several hours and therefore do not relieve the initial symptoms and signs. This is undesirable for the management of anaphylactic shock, a life-threatening emergency situation in which immediate onset of action is necessary.

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Chapter 25

Drugs for Gout

CASE 1: DRUG THERAPY OF ACUTE GOUT

Mr RW, a 45-year-old obese male was awakened at 3 o'clock in the night by severe excruciating pain in his big toe. Even, the weight of the bedsheet made him scream in pain. Next day, he consulted the doctor. On examination, there was redness, swelling and warmth of the metatarsophalangeal joint. He is a chronic smoker and an alcoholic. Medical history suggests dyspepsia and gastritis. He admitted that he had participated in walkathon the previous day.

He was diagnosed as a case of acute gout and initiated treatment with a short course of ibuprofen 800 mg now and every 8 hours until resolution of symptoms (usually 7–10 days).

Qa. Explain the signs and symptoms which are consistent with the diagnosis of acute gout as in RW.

There was sudden onset of intense pain in the early hours of the morning in a single joint commonly affecting the base of the great toe (first metatarsophalangeal joint) associated with redness and swelling. Risk factors predisposing to acute gout are obesity, alcohol consumption and increased physical activity prior to the precipitation of symptoms of acute gout.

Qb. Mention the therapeutic goal in the management of acute gout. What are the pharmacotherapeutic options for the treatment of acute gout?

The therapeutic goal in acute gout is to control pain using drugs that suppress inflammation due to precipitation of urate crystals in the joint.

The treatment options for acute gout are the following:

1. Non-steroidal anti-inflammatory drugs (NSAIDs):
2. Colchicine
3. Glucocorticoids

Qc. Which NSAIDs are used in the treatment of acute gout?

NSAIDs such as naproxen (500 mg, twice daily) or indomethacin (50 mg, three times daily) are potent and commonly used non-selective NSAIDs in the management of acute gout. Other orally-administered NSAIDs that may be used include ibuprofen, diclofenac, meloxicam and celecoxib.

Qd. What are the important contraindications for use of NSAIDs in acute gout?

The important contraindications to NSAIDs include:

1. Chronic kidney disease (CKD) with creatinine clearance (CrCl) of less than 60 ml/min per 1.73 m^2
2. Active duodenal or gastric ulcer
3. Cardiovascular disease particularly heart failure or hypertension that is difficult to control. Caution is necessary in patients with known cardiovascular disease or with multiple risk factors for atherosclerotic coronary disease.
4. NSAID allergy
5. Ongoing treatment with anticoagulants.

Qe. Do you think, the use of non-selective NSAID such as ibuprofen is a reasonable treatment option in case of RW, given that there is history of dyspepsia and gastritis?

NSAIDs are considered to be appropriate particularly in younger patients (less than 60-years-old) who lack renal, cardiovascular, or active gastrointestinal disease.

It is well documented that use of non-selective NSAIDs is associated with GI complications. COX-1 enzyme produces prostaglandins that protect the stomach and intestinal lining and inhibition of COX-1 enzyme increases the incidence of peptic ulcer disease and gastrointestinal bleeding.

The risk is high with longer-acting NSAIDs such as piroxicam and ketorolac, with naproxen conferring the moderate risk and ibuprofen lower risk of GI toxicity. Therefore, ibuprofen may be used with caution in RW to provide symptomatic relief of pain arising from inflamed joint.

Qf. Is celecoxib, a selective COX-2 inhibitor, better alternative to non-selective COX (COX-1 and COX-2) inhibitors in the management of episode of acute gout? Explain with reasons.

Theoretically, selective COX-2 inhibitors appears to be a better alternative to non-selective COX inhibitors because they have limited inhibitory action on COX-1 enzyme thereby it continues to act producing prostaglandins that protect the gastric mucosa and reduces gastric injury while exerting its anti-inflammatory action through inhibition of COX-2.

Celecoxib (selective COX-2 inhibitor) at doses of 200 mg twice daily has been demonstrated to be useful in pain relief. However, celecoxib can increase risk of fatal heart attack or stroke. It may also cause stomach or intestinal bleeding which can be fatal. It is not specifically approved by FDA and caution should be advised when used in patients with history of peptic ulcer disease.

CASE 2: TREATMENT OF GOUT FLARES

WJ, a 50-year-old obese female admitted to the hospital had undergone gallstone surgery. On the 5th day of the postoperative period she experienced pain, redness and swelling in her elbow accompanied with fever and chill. 2 years ago she was diagnosed with gout and was suspected to have gout flare and treatment was initiated. She is a known case of diabetes and her blood glucose is under control with insulin therapy. The renal function tests of WJ is normal.

Qa. Considering the clinical setting of WJ, which treatment option would you choose, corticosteroids or NSAIDs?

NSAIDs are preferred over glucocorticoids in patients who have diabetes and are in postoperative period in whom glucocorticoids may increase risk of impaired wound healing.

Caution in the initiation of oral glucocorticoid therapy is necessary when recurrent gout flare is accompanied by fever, chills, or other systemic symptoms or clinical signs giving rise to the suspicion of intercurrent infection. Glucocorticoids can raise the risk of infections because although they are effective in reducing inflammation and symptoms, they have a wide range of effects on the immune system.

WJ is young (less than 60 years old) and lacks renal, cardiovascular, or active gastrointestinal disease. A reasonable alternative to oral glucocorticoids, is a potent oral NSAID, such as naproxen (500 mg, twice daily) or indomethacin (50 mg, three times daily).

Qb. Although aspirin is an NSAID, it is not used in the treatment of gout flares. Explain with reasons.

Aspirin is a non-steroidal anti-inflammatory drug widely used for the relief of pain and inflammation. But it is not used for the treatment of gout flares because at low doses of less than 2 to 3 g/day, aspirin results in renal uric acid retention with subsequent increase in serum uric acid level and precipitation of gout.

CASE 3: USE OF CORTICOSTEROIDS AND COLCHICINE IN ACUTE GOUT

LS, a 71-year-old woman, developed acute polyarticular arthritis with involvement of knee, ankle and elbow joints and was admitted to the hospital 20 days after she underwent a living-donor renal transplant for haemodialysis-dependent renal dysfunction. Medications post-transplantation included metoprolol, trimethoprim-sulfamethoxazole, cyclosporine and prednisone. Her renal failure resulted from long-standing hypertension. Past-medical history included known hyperuricaemia and gout, previously treated with daily colchicine for several years. Synovial fluid analysis and culture shows uric acid crystals and absence of joint infection.

The gout flare of LS was treated with an increased dose of oral prednisone at 60 mg daily for 4 days with prompt improvement, then tapered to 30 mg daily over the course of 10 days. Colchicine 0.6 mg daily was restarted on the day of admission as prophylaxis to prevent further gout attacks.

Qa. For the treatment of acute gout attack, LS was given oral prednisone at 60 mg daily for 4 days followed by tapering to 30 mg daily over the course of 10 days. Justify the treatment.

Oral corticosteroids may be particularly useful for elderly patients with polyarticular joint involvement in an established case of gout. Corticosteroid adverse effects (e.g. osteoporosis, myopathy, peptic ulcer disease, central nervous system effects, HTN, predisposition to infections) are not likely with short courses of treatment for gout attacks. Slower tapering of steroids is useful to avoid rebound flares that are relatively common once corticosteroids are withdrawn.

Qb. Can glucocorticoids be administered intravenously in a clinical situation described for LS?

In hospitalized patient with polyarticular involvement with existing or easily established intravenous access with no contraindications to glucocorticoids, and/or who is unable to take oral medication, intravenous administration of a parenteral glucocorticoid such as methylprednisolone can be considered as an option.

Qc. Can intra-articular glucocorticoids be considered as an option for the treatment of gouty arthritis of LS?

Arthrocentesis with joint fluid aspiration and intra-articular injection of glucocorticoids may be preferred for a patient of established gout with one or two actively inflamed joints for whom the likelihood of infection is excluded and/or who are unable to take oral glucocorticoids. Triamcinolone acetonide may be used for joint injection. LS is the case of acute polyarticular arthritis with multiple joint involvement and thus is not a candidate for intra-articular glucocorticoids.

Qd. How does colchicine act in gout?

Colchicine: Binds to intracellular protein 'tubulin' and prevents polymerisation and formation of microtubules which play an important role in cell trafficking. Colchicine suppresses neutrophil activation which includes decreased release of chemotactic factor inhibiting the migration of neutrophils into the joint and adhesion to the joint capsule.

Qe. How does pharmacodynamic and pharmacokinetic properties of colchicine relate to gastrointestinal side effects of colchicine in gout treated patients?

Cochicine by preventing the formation of microtubules *inhibits cell division and mitosis*. Therefore, when it comes in contact with the epithelium of gastrointestinal tract inhibits the turnover of epithelial cells.

Colchicine *undergoes enterohepatic cycling* which includes secretion of drugs into the bile which is released into the GI tract during the digestive processes, absorbed into the portal circulation followed by reuptake into the liver and released again into the intestine. The repeated delivery of the drug into the intestine. The enterohepatic cycling prolongs the half life of the drug and repeated delivery to the intestine increases the incidence of diarrhea.

Qf. What precaution will you take to reduce the side effects associated with cochicine administered in the patient LS?

High-dose colchicine dosing regimens (persistent hourly doses until resolution of flare) are discouraged because of unacceptably high toxicity. The most common adverse effects of cochicine, diarrhea and abdominal cramping are less in patients who receive no more than 1.8 mg in total on the first day compared with patients receiving higher doses, such as 0.6 mg every one to two hours until symptom relief or intolerance. The patient LS was instructed to take colchicine 0.6 mg daily, which is a low dose and is less likely to cause adverse effects.

Qg. How would you expect colchicine to interact with cyclosporine when used concurrently as in case of LS who has undergone organ transplant? What should be the line of action to reduce the risk of drug interaction?

Colchicine is the substrate for both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein. CYP3A4 is found in hepatocytes and transforms colchicine to inactive metabolites. P-gp is found in epithelial cells lining the gastrointestinal tract, kidney proximal tubules, bile duct membrane and the blood–brain barrier. Inhibition of P-gp within the intestinal lumen increases colchicine bioavailability and inhibition at bile ductile membrane and kidney tubules decreases cochicine clearance.

Cyclosporine is a potent inhibitor of both CYP3A4 and P-gp, therefore co-administration of colchicine with cyclosporine increases the risk for toxicity. Colchicine has a narrow therapeutic margin and drug accumulation is associated with severe and sometimes fatal consequences.

Prescribers should perform regular assessments of drug interactions, organ function, and other factors that can influence serum concentrations and prescribe a reduced dose and/or frequency when warranted or consider change in medication if necessary.

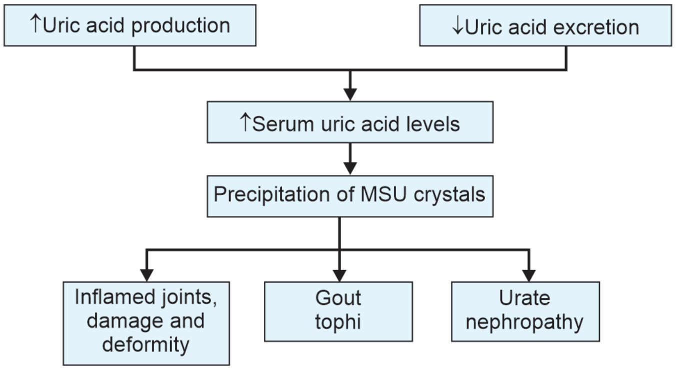
CASE 4: DRUG THERAPY OF CHRONIC GOUT

Mr WX diagnosed 3 years ago with gout, experienced 2 to 3 attacks of pain in a year and learnt to manage his pain with indomethacin. Recently, the pain attacks started occurring at shorter intervals and failed to subside with analgesics. He presented to the doctor with complains of continuous pain involving the toe, knee and ankles.

On examination, there were nodules near the olecranon in the elbow and ears. Aspiration of joint fluid finds needle-shaped uric acid crystals. The synovial fluid appeared cloudy.

He was prescribed naproxen which resulted in reduction in pain and swelling in the joint and thereafter it was stopped. Past medical treatment included allopurinol which was continued during the period of acute attack of gout and colchicine was started with allopurinol as prophylaxis to prevent further gout flares.

Qa. What are the manifestations of hyperuricaemia in long term in chronic gout? What are the signs and symptoms of gout getting worse in case of WX?



MSU: Monosodium urate crystals

Fig. 25.1: Pathophysiology of gout

Gout is a disorder of purine metabolism and occurs when its final metabolite, uric acid is persistently elevated in the blood. At high levels uric acid crystallizes and the crystals deposit in joints, tendons, and surrounding tissues resulting in an acute attack of gout. The deposition of urate crystals in the kidney can cause renal impairment and failure.

The signs that gout may be getting worse in case of WX are the following:

- Gout flares or acute gout attacks happened more often, lasted longer and failed to subside with analgesics.
- Involvement of multiple joints including toe, ankles and knee in chronic gout, in contrast to single joint involvement in the early phase of the disease.
- Uric acid crystals may start to collect in soft tissue forming lumps called tophi in chronic gout. These have appeared in the elbow and ears in case of WX.
- Kidney problems can also arise due to formation of stones and damage to the kidney. But this is not seen in case of WX.
- WX was on treatment with allopurinol, a urate lowering therapy that is prescribed when the attacks become recurrent within short intervals and there is tophi deposition.

Qb. What is the therapeutic objective of initiating urate lowering therapy in chronic gout?

Management of chronic gout is targeted on lowering and maintaining serum uric acid at subsaturation concentration below 6 mg/dl.

Qc. What are the various ways of lowering the serum uric acid levels? Mention the urate lowering therapies available for the management of gout.

Serum uric acid can be lowered by reducing the uric acid production and decreasing the uric acid excretion. Urate lowering therapies available for the treatment of gout can broadly be grouped into:

- Xanthine oxidase inhibitors: Allopurinol and Febuxostat
- Uricosuric agents: Probenecid, sulfinpyrazone and benzbromarone
- Newer agents: Pegloticase and rasburicase (recombinant uricases)

Qd. Although allopurinol, a urate lowering drug, has no proven benefit in acute gout, it is continued during the acute phase of gout. Explain with reasons.

In patients already receiving allopurinol at the time of gout flare, the medication should be continued without interruption. Discontinuation of allopurinol during the acute phase of gout and then reintroduction of the drug later causes sudden decrease in uric acid synthesis accompanied with urate lowering and dissolution of crystal deposits. This disrupts urate homeostasis and increases the risk of gout attacks.

Qe. What should be the line of action to prevent the occurrence of gout flares while initiating treatment with allopurinol?

Any urate lowering therapy should not be started during an acute attack, since the dissolution of crystal deposits increases the risk of gout attacks. An NSAID or cochicine is administered during the first 4 to 6 months of initiation of allopurinol therapy to reduce the chance of precipitation of an acute attack of gout. Also allopurinol should be started at a low dose and titrated up to the effective dose to avoid the 'crash' reduction of uric acid.

CASE 5: TREATMENT OF CHRONIC GOUT WITH ALLOPURINOL

TN, an 80-year-old woman suffering from recurrent gouty arthritis for over 5 years. She is a known case of diabetes, hypertension and moderate chronic kidney disease and was on medications for the mentioned problems.

For gout treatment, 3 years earlier she was started on allopurinol. 2 months after starting allopurinol she developed itching, rash and fever. Allopurinol was stopped immediately and her signs and symptoms improved. Probenecid is started at an initial dose of 250 mg twice daily and gradually increased. It failed to cause significant lowering of serum uric acid levels at maximum effective dose.

Qa. Comment on the possible drug interaction based on the clinical presentation described in case of patient TN.

The adverse event in case of TN manifests as rash, itching, fever, and deterioration of kidney function. The immediate discontinuation of the drug was followed by relief of signs and symptoms.

The adverse event was most likely due to allopurinol and is known as allopurinol hypersensitivity syndrome (AHS). This can lead to skin necrosis, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and even death.

Allopurinol hypersensitivity is primarily mediated by an oxypurinol, metabolite of allopurinol-mediating T-cell sensitization. Risk factors for allopurinol-related serious adverse events include recent introduction of allopurinol, the presence of the *HLA-B 58:01* allele, a higher starting dose, renal impairment and the concomitant use of diuretics.

In patients with renal impairment such as in case of TN, allopurinol should be started at a low dose with slow titration and close monitoring of the patient by regular follow-up and educating the patient about the possible allopurinol-related adverse drug reactions with timely management of the adverse drug reaction.

Qb. How would you think pre-existing chronic kidney disease in case of TN could have impacted the pharmacological action of probenecid, used in place of allopurinol for gout treatment?

Probenecid, a uricosuric drug, is a second-line drug to xanthine oxidase inhibitor, for chronic gout patients, when there is contraindication, intolerance or drug interaction with xanthine oxidase inhibitor such as allopurinol.

Uricosuric drugs act by enhancing the excretion of uric acid by inhibiting its active reabsorption from the renal tubule. This action is blunted in presence of renal dysfunction and the drug may not be effective. Hence, uricosuric drugs should not be used in renal insufficiency.

Qc. Allopurinol should not be administered with azathioprine. Give reasons.

Allopurinol produces its therapeutic effect by inhibiting xanthine oxidase which causes purine degradation into uric acid.

Enzyme xanthine oxidase plays a role in the metabolism of azathioprine and 6-MP.

When both drugs are administered together, allopurinol by inhibiting xanthine oxidase may interfere with the metabolism of azathioprine and 6-MP which are metabolised by the same enzyme. Therefore, the dose of mercaptopurine or azathioprine should be reduced by approximately 75% or switching from azathioprine to non-purine immunosuppressive drug such as mycophenolic acid, is another option.

CASE 6: TREATMENT OF GOUTY ARTHRITIS WITH FEBUXOSTAT

TN, in the past one year, frequency and severity of gout attacks increased with tophaceous deposits in the subcutaneous tissues. Her renal function was deteriorated to GFR 30 ml/min. There is history of hypersensitivity reaction to allopurinol.

She was prescribed febuxostat instead of benzbromarone to reduce the effects of hyperuricaemia. On monitoring the patient, it was observed that in 2 weeks, there was a reduction in serum urate levels with gradual improvement of GFR and resolution of tophaceous deposits. The quality of the life of the patient improved over a period of time.

Qa. How would you justify that febuxostat was appropriate for the management of her complications of gouty arthritis?

In case of TN, uricosuric drugs cannot be used because her renal function has declined and allopurinol is not suitable because of serious hypersensitivity syndrome related to allopurinol. Febuxostat, a non-purine xanthine oxidase inhibitor, can be used as an alternative to allopurinol for chronic management of hyperuricaemia in patients with gout.

Febuxostat is chemically distinct to allopurinol and metabolized by the liver and excreted via both liver and kidney unlike allopurinol that is completely excreted through the kidneys. It does not require dose adjustments for CrCl greater than 30 ml/minute. It is more selective than allopurinol for xanthine oxidase and does not inhibit other enzymes involved in purine and pyrimidine metabolism.

Qb. What are the safety concerns related to the use of febuxostat for the long-term management of gout?

In general, febuxostat is well tolerated in clinical trials. However, some concerns were raised regarding elevation of liver enzymesin 3–5% of patients. Febuxostat has been reported to have caused cardiovascular events and hence caution is recommended in patients with ischaemic heart disease or severe congestive heart failure.

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Chapter

26

Drugs for Rheumatoid Arthritis

CASE 1: PATHOPHYSIOLOGY AND DRUG THERAPY OF EARLY RHEUMATOID ARTHRITIS

A 32-year-old female AB, presents to rheumatology outpatient department with complaints of pain, swelling and tenderness in the metacarpophalangeal joints (1–3) on both sides, for past 1 month.

Laboratory investigations revealed presence of anti-citrullinated peptide antibodies (ACPA) and raised erythrocyte sedimentation rate (ESR).

You have diagnosed AB as a case of rheumatoid arthritis based on clinical signs and symptoms and laboratory reports.

Treatment prescribed: **Methotrexate at a dose of 15 mg once a week for 3 months and methylprednisolone 5 mg/day for a month.**

Qa. Describe the pathophysiology of rheumatoid arthritis using a schematic diagram.

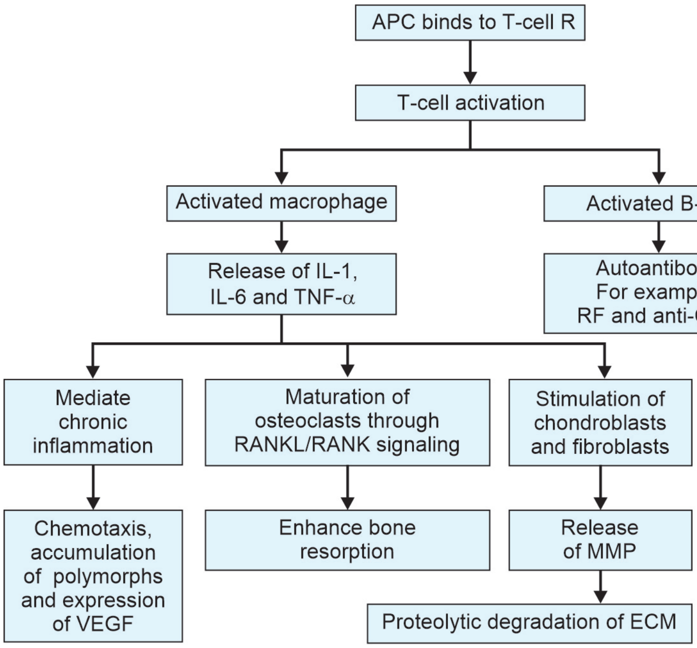
Rheumatoid arthritis (RA) is characterized by synovial inflammation and hyperplasia, autoantibody production such as rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA), cartilage and bone destruction and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders.

RA develops when a genetically susceptible individual experiences an external trigger (e.g. cigarette smoking, infection or trauma) an autoimmune reaction is activated. The initiating interaction for an autoimmune response takes place between antigen-presenting cells (APC) and the T-cell receptor, leading to activation of T lymphocytes.

The activated T-cell induces B-cell differentiation and formation of autoantibodies such as rheumatoid factor (RF) and anticitrullinated protein (ACPA) antibody which further accelerates the autoimmune process.

The monocyte and macrophage activation results in dysregulated persistent production of pro-inflammatory cytokines including IL-1, IL-6, TNF-α which play a pivotal role in chronic inflammation characterized by accumulation of polymorphonuclear leukocytes, increased vascular permeability and pannus formation.

Osteoclasts are the key cells which induce bone resorption by enhanced expression of RANKL receptor. Stimulation of chondrocytes and fibroblasts in the synovial lining release matrix metalloproteinases (MMP). These are proteolytic enzymes responsible for joint destruction in RA through breaking down various extracellular components including proteoglycans and fibrous proteins (collagen, elastin, laminin and fibronectin).


APC binds to T-cell R
T-cell activation
Activated macrophage
Activated B-cell
Release of IL-1, IL-6 and TNF-α
Autoantibody For example: RF and anti-CCP
Mediate chronic inflammation
Maturation of osteoclasts through RANKL/RANK signaling
Stimulation of chondroblasts and fibroblasts
Chemotaxis, accumulation of polymorphs and expression of VEGF
Enhance bone resorption
Release of MMP
Proteolytic degradation of ECM

APC: Antigen-presenting cell; R: Receptor: RF: Rheumatoid factor;
CCP : Cyclic citrullinated peptide antibodies; MMP: Matrix metalloproteinases;
VEGF: Vascular endothelial growth factor; ECM: Extracellular matrix

Fig. 26.1: Pathophysiology of rheumatoid arthritis

Qb. What are the treatment goals in the management of patients with rheumatoid arthritis?

Treatment goals of rheumatoid arthritis are as follows:

1. Suppression of disease activity and rapid reduction of symptoms (no tender or swollen joints)
2. Preventing joint damage (structural damage and deformity)
3. Improvement in laboratory indices.
4. No radiological progression.
5. Normal quality of life and normal participation in social and occupational activities.
6. None or lower levels of comorbidities.

Qc. What are the treatment options available for the management of rheumatoid arthritis?

Management treatment options for rheumatoid arthritis as per guidelines are:

1. Disease-modifying antirheumatic drugs (DMARDs)
2. Anti-inflammatory drugs: Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.
3. Combination therapies
4. Biologicals

Qd. What are the available drugs and how do the drugs act in the management of rheumatoid arthritis?

S. No.	*Drug class*	*Primary action*
I.	**DMARD (conventional/traditional)** Methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF) **Other less commonly used DMARDs** • d-Penicillamine • Gold	**MTX:** Inhibits replication and function of T cells because of selective inhibition of DNA synthesis **SSZ:** Sulfapyridine, the active component in treatment of RA suppresses the release of cytokines by inflammatory cells **HCQ:** Inhibition of antigen processing and presentation **LEF:** Inhibits dihydro-orate dehydrogenase, reduces ribonucleotide synthesis and thereby inhibits cell growth and T-cell proliferation
II.	**Anti-TNF biologic therapy** Adalimumab, etanercept, certolizumab, infliximab	TNF is a potent inflammatory cytokine produced mainly by macrophages and monocytes thus contributing to the inflammatory and destructive changes that occur in RA Blockade of TNF results in a reduction in a number of other pro-inflammatory cytokines (IL-1, IL-6, and IL-8)
III.	**Non-TNF biologic therapy** Abatacept, rituximab, tocilizumab, anakinra	**Abatacept:** T-cell co-stimulatory blockade (prevents the binding of CD80 and CD86 ligands on the surface of APCs to the CD28 receptor on the T-cell) **Rituximab:** Depletes B cell, so they cannot act as antigen presenting cells to activate T cells. The autoantibody production is inhibited **Tocilizumab:** Humanised monoclonal antibody directed against IL-6 recepter (IL-6 is a proinflammatory cytokine causing acute phase response, cytokine production and osteoclast activation) **Anakinra:** IL-1 R antagonist
IV.	**Tyrosine kinase inhibitors (JAK-STAT inhibitors)** Tofacitinib, barcitinib	Block the cytokine signalling pathway, suppress the release of cytokines
V.	**Anti-inflammatory drugs** Aspirin and other NSAIDs	Inhibit cyclo-oxygenase pathway and inhibit the production of prostaglandins
VI.	**Anti-inflammatory and immunomodulatory drugs** Glucocorticoids	Steroid hormones suppress immunostimulatory functions and exerts anti-inflammatory effects by up-regulating the expression of anti-inflammatory proteins in the nucleus and represses the expression of proinflammatory proteins in the cytosol
VII.	**Immunosuppressants** Azathioprine, cyclosporine, mycophenolate mofetil (MMP)	Suppress the immune system and reduce the impact of the autoimmune disease on the body

Qe. Mention the role of disease modifying anti-rheumatic drugs (DMARDs) in the management of rheumatoid arthritis.

Disease modifying antirheumatic (DMARDs) are effective in controlling the articular symptoms of rheumatoid arthritis and also modify the progression of the disease by reducing joint damage and deformity, radiographic progression and long-term disability associated with rheumatoid arthritis. However, they are slow-acting and thus immediate effects are not seen.

Qf. Justify the selection of methotrexate as initial DMARD therapy for the treatment of rheumatoid arthritis.

Methotrexate is preferred as initial DMARD therapy for patients with rheumatoid arthritis because it has a rapid onset (usually 1–2 months), a high efficacy, rate at managing symptoms, slowing disease progression, relatively low cost and toxicity, and a long history of successful use.

Qg. AB was advised to take 5 mg of oral folic acid on the morning following the day of methotrexate administration. Explain the reasons for folic acid supplementation with methotrexate therapy.

Methotrexate inhibits dihydrofolate reductase which catalyses reduction of dihydrofolate (DHF) to tetrahyrofolate which is an important cofactor in the production of purines and pyridines in T cells. Therefore, methotrexate induces reduction in T-cell proliferation and exhibits immunosuppressant and anti-inflammatory effects in RA.

While methotrexate is effective in the treatment of rheumatoid arthritis, it is commonly discontinued due to adverse effects, which are thought to be mediated via folate antagonism. MTX-related adverse effects include GI disturbances, mucositis (mouth or GI ulcerations), alopecia, anaemia and LFT elevations.

The use of supplemental folic acid in RA patients treated with methotrexate has been shown to improve continuation rates by reducing the incidence of liver function test abnormalities and gastrointestinal intolerance. Furthermore, supplemental folic acid offsets the elevation in plasma homocysteine, associated with the use of methotrexate. This may in turn reduce the risk of cardiovascular disease.

Qh. What is the therapeutic basis of using glucocorticoids with methotrexate, a synthetic DMARD for the treatment of rheumatoid arthritis?

Glucocorticoids have immunosuppressant and anti-inflammatory actions that slow the progression of damage to the joints in rheumatoid arthritis. They provide quick symptomatic relief of pain and fever while conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) have a slow onset of action and may require 2–3 months to achieve a full therapeutic response. To bridge the time between the initial prescription of DMARDs and the clinical response, short term use of oral corticosteroid therapy is necessary in early rheumatoid arthritis with moderate to high disease activity.

In contrast, the physician should be mindful that corticosteroids are usually not needed when biologic DMARDs are used. The reason is that biologic DMARDs have a rapid onset of action and infection risk may be potentiated if used concomitantly with corticosteroids.

Qi. How can we achieve a positive benefit–risk ratio when using glucocorticoids in the treatment of patients with rheumatoid arthritis?

Low dose and short-term use of corticosteroids in rheumatoid arthritis is a common treatment protocol. Steroids are usually taken in the morning as it mimics the timing of our body’s own production of cortisone.

Long-term use of glucocorticoids, especially at doses >5 mg/d, should be avoided because of the potential occurrence of adverse effects. As soon as, the disease being treated is under control, glucocorticoids should be gradually reduced and ultimately stopped ideally within 3–6 months. Tapering must be done carefully to avoid both recurrent activity of the underlying disease and possible cortisol deficiency resulting from hypothalamic-pituitary-adrenal axis suppression during the period of steroid therapy.

CASE 2: DRUG THERAPY WITH BIOLOGIC DMARDS FOR THE MANAGEMENT OF PROGRESSIVE RHEUMATOID ARTHRITIS

A 54-year-old obese female PW, a known case of rheumatoid arthritis for 5 years, presents to the tertiary care hospital with complaints of pain and severe inflammation in multiple small and large joints which is symmetrical in nature and early morning stiffness for past one month. She was not relieved of her symptoms with analgesics such as diclofenac. In addition, her current medications include methotrexate and hydroxychloroquine (HCQ). She is a known case of type 2 diabetes mellitus, hypertension and dyslipidaemia.

Modification in treatment regimen was discussed with PW and treatment was switched to adalimumab (TNF-α inhibitor) 40 mg, 2 injections subcutaneously every other week with methotrexate 15 mg/wk.

Qa. Prior to initiating treatment with adalimumab, the following investigations were ordered. What is the clinical significance of the following investigations?

1. **Tuberculin skin testing with purified protein derivative (PPD) or interferon gamma release assay (IGRA) blood test**
2. **Hepatitis B virus screening**
3. **Liver function test**
4. **Complete blood count (CBC)**

Patients taking TNF-α inhibitors are at increased risk for serious infectious events, including tuberculosis and infections caused by opportunistic pathogens. TNF-α regulates host defences against mycobacterial infection, therefore patients receiving TNF-α inhibitors are at increased risk for new-onset tuberculosis and tuberculosis reactivation.

- Tuberculin skin testing with purified protein derivative (PPD) or interferon gamma release assay (IGRA) blood test detects latent TB.
- Hepatitis B virus screening is important as hepatitis B virus reactivation can occur in patients treated with biologics resulting in liver failure and death.
- Liver function tests help to detect damage caused to the liver by the drugs. Liver enzyme test can help determine if hepatitis B virus has been reactivated
- Complete blood count (CBC): This test monitors white blood cells which fight infections, platelets, and red blood cells. CBC commonly demonstrates anaemia and correlates with disease activity; it improves with successful therapy.

Qb. Should vaccination be a consideration while deciding to initiate therapy with csDMARD or bDMARD for a patient with rheumatoid arthritis? If yes, which vaccines are recommended by ACR prior to therapy?

Yes, it is recommended that patients receive the following vaccinations prior to the initiation of csDMARD or bDMARD therapy: Pneumococcal, influenza, hepatitis B, human papillomavirus, and herpes zoster.

Qc. Why is it important for the physician to monitor the cardiovascular status prior to initiation and during treatment with biologic DMARDs for the management of rheumatoid arthritis?

Evidence suggests that RA is associated with increased risk of cardiovascular morbidity and mortality. Although the traditional risk factors such as diabetes, hypertension, dyslipidaemia contribute to cardiovascular mortality, there is increased role of inflammatory processes in the development and progression of atherosclerosis leading to cardiovascular events in RA. In addition, therapy with biologic DMARDs increases the risk for cardiovascular events with certain drugs.

While considering treatment of RA, it is recommended that anti-TNF therapy should not be used for RA patients with moderate-to-severe (New York Heart Association [NYHA] class III and IV) heart failure. In mild (NYHA class I and II) heart failure, anti-TNF therapy can be used with caution, but patients should be closely monitored for cardiac decompensation. Blood glucose and lipid profile testing should be done at regular intervals to address the risk factors for coronary artery disease.

Case Continued

Two months later, PW returned to the clinic to consult her physician regarding her preference for oral agents in the management of rheumatoid arthritis and wanted to know whether adalimumab could be substituted for an oral anti-rheumatic drug.

Qa. Does the physician have any alternative treatment option to parenteral biologic DMARDs?

The physician informs PW about tofacitinib, a potent, selective JAK inhibitor that preferentially inhibits Janus kinase. It is administered orally 5 mg twice daily and is indicated for the treatment of moderate-to-severe active rheumatoid arthritis.

Qb. Mention the adverse effects related to injectable bDMARDs that reduces adherence to treatment.

Infusion reactions may lead to discontinuation of infliximab therapy administered intravenously. Injection site reactions (ISR) have been reported for etanercept, adalimumab, certolizumab and golimumab administered subcutaneously.

Qc. What is the role of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of rheumatoid arthritis?

Non-steroidal anti-inflammatory drugs (NSAIDs) are used only for a brief period for immediate relief of symptoms of pain and inflammation during severe disease activity while awaiting the onset of action of disease modifying antirheumatic drug (DMARD) because the DMARDs are known to have a slow onset of action.

NSAIDs have no role in modifying the progression of the disease. AB was prescribed diclofenac which is a non-selective reversible inhibitor of COX enzyme (COX-1 and COX-2), that mediates the synthesis of prostaglandins responsible for pain and inflammation. This accounts for the analgesic and anti-inflammatory action of diclofenac in rheumatoid arthritis.

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Chapter

27

Drug Therapy for Pain

CASE 1: A CASE OF ACUTE INFLAMMATORY PAIN

A 49-year-old male patient 'AB', twisted his ankle while he was hurriedly climbing the staircase. After the ankle injury, he took paracetamol for pain relief. Gradually, he developed redness, swelling, tenderness and there was decreased range of motion at the ankle joint despite use of paracetamol.

Qa. Explain the pathway responsible for the transmission of pain signals from the periphery to the brain.

In response to thermal, mechanical and chemical event, proinflammatory autacoids such as prostaglandins, substance P, bradykinin, TNF-α and interleukins are released that activate the peripheral sensory neurons (nociceptors) and lead to the generation of action potential which travels along the primary afferent neuron to the substantia gelatinosa of the dorsal horn of the spinal cord. Subsequently, the nociceptive signals are transmitted across the synaptic connections along the secondary afferent neuron forming the spinothalamic tract carrying the pain signals upwards to the cerebral cortex that perceives pain.

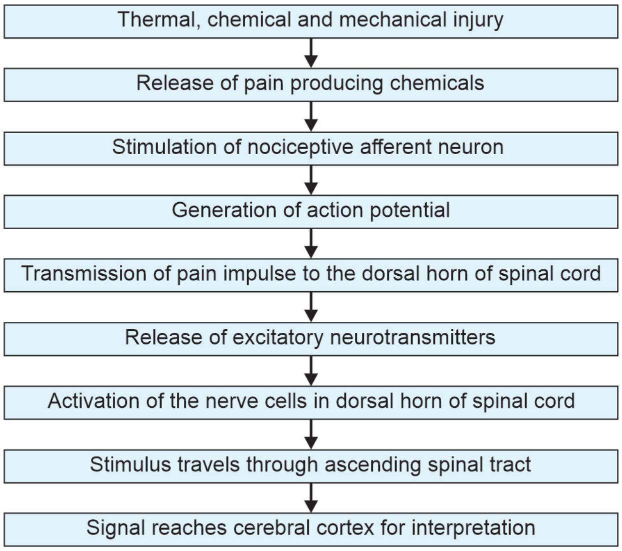

Thermal, chemical and mechanical injury
Release of pain producing chemicals
Stimulation of nociceptive afferent neuron
Generation of action potential
Transmission of pain impulse to the dorsal horn of spinal cord
Release of excitatory neurotransmitters
Activation of the nerve cells in dorsal horn of spinal cord
Stimulus travels through ascending spinal tract
Signal reaches cerebral cortex for interpretation

Fig. 27.1: Pain transmission pathway from periphery to the cerebral cortex

Qb. How is paracetamol useful in case of AB?

Paracetamol is an *effective analgesic agent and is considered the safest choice* in the management of musculoskeletal pain. Paracetamol is thought to inhibit prostaglandin synthesis in the central nervous system, which explains its analgesic and antipyretic activity. It has no action on peripheral prostaglandins and hence devoid of gastrointestinal, renal and cardiovascular toxicities. So, it is well-tolerated.

Qc. What could be the reason for failure to respond to treatment with paracetamol in case of AB? What are the alternative drugs available for managing pain in this case?

Since paracetamol *lacks anti-inflammatory effect*, it may not relieve redness, swelling and tenderness arising as a consequence of inflammation. Paracetamol can be substituted with a non-selective anti-inflammatory drug such as naproxen, diclofenac, etoricoxib, indomethacin, meloxicam, ibuprofen. Unlike paracetamol, they not only serve as an analgesic and antipyretic but also exert anti-inflammatory action, which is essential for the management of severe inflammatory pain.

Qd. How do NSAIDs act in relieving pain and inflammation?

Non-steroidal anti-inflammatory drugs (NSAIDs) are *non-selective inhibitors of cyclo-oxygenase (COX-1 and COX-2).* Inhibition of COX-1 blocks prostaglandin-mediated inflammatory response and pain signals. Suppression of COX-2 overexpression at the inflammatory sites further adds to the therapeutic effect.

Qe. Which NSAID would you select, if:

i. AB is at increased risk of gastrointestinal bleeding?
ii. AB has cardiovascular risk factors?
iii. AB has low risk of gastrointestinal and cardiac toxicity?

i. Etoricoxib is the preferred choice among NSAIDs, if AB is at increased risk of gastrointestinal bleeding. It is prescribed along with proton-pump inhibitor.

ii. Naproxen is preferred for AB in presence of cardiovascular risk factors.

iii. Any non-selective NSAID and proton pump inhibitor or COX-2 selective NSAID can be used if AB has low risk of gastrointestinal and cardiac toxicity.

Qf. What side effects are likely to occur with non-selective NSAIDs due to action on cyclo-oxygenase enzyme?

Both therapeutic and side effects of NSAIDs are dependent on cyclo-oxygenase inhibition. All NSAIDs that are *non-selective inhibitors of cyclo-oxygenase enzyme* (COX-1 and COX-2) have significant *adverse effects on gastric mucosa and renal parenchyma.*

Prostaglandins (PGE2 and PGI2) play a key role in the protection of gastric mucosal cells by increasing the blood flow to the gastric mucosa and stimulating the secretion of mucus and bicarbonate. Prostaglandins also regulate the renal blood flow to the kidney. Blocking prostaglandins may lead to decreased blood flow to the kidneys causing acute kidney injury and increased risk of gastric ulcerations and bleeding due to loss of gastroprotective effect.

Qg. In terms of adverse effects, what are the advantages of selective COX-2 inhibitors over non-selective inhibitors of cyclo-oxygenase enzyme? Mention the potential risks associated with COX-2 inhibitors.

COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib), specifically inhibit the COX-2 isoenzyme. This selectivity spares the inhibition of COX-1 which is thought to mediate the integrity of the gastric mucosa, normal platelet function and regulate renal blood flow. Therefore, COX-2 inhibitors have *less potential for GI and haematological side effects* seen with traditional NSAIDs.

High dose, chronic users of selective COX-2 inhibitors, *have increased risk of acute myocardial infarction and sudden cardiac death*.

Qh. How would you differentiate the actions of NSAIDs from opioids used as analgesics?

Non-steroidal anti-inflammatory drug is more effective analgesic in the treatment of musculoskeletal pain with inflammation than opioid analgesics which are mainly used to treat deep seated visceral pain.

In terms of adverse effects, NSAIDs such as aspirin do not produce CNS depression, respiratory depression and drug dependence which are common with opioids. However, gastrointestinal side effects are associated with use of NSAIDs.

CASE 2: PARACETAMOL-INDUCED HEPATOTOXICITY

AB presents to the emergency department with the chief complaints of nausea and emesis. He informed that he has been taking approximately 8 tablets of extra strength 500 mg paracetamol each, over the course of the day, every day, for the past 2 weeks for pain relief from the recent ankle injury sustained during a fall.

Physical examination:

- **Febrile (99.4F)**
- **Left upper abdominal tenderness with evidence of mild hepatomegaly and mild sclera icterus.**

Laboratory analysis revealed markedly elevated serum ALT—537 IU/L and AST—433 IU/L, respectively, increased bilirubin—40 µmol/L and a low serum glucose level of 2 mmol/L.

The case was diagnosed as 'paracetamol-induced hepatotoxicity'.

Qa. What is the underlying mechanism for paracetamol-induced hepatotoxicity as in case of AB?

At therapeutic doses, less than 5% of acetaminophen is metabolized by the cytochrome P (CYP)-450 system to N-acetyl-*p*-benzoquinone-imine (NAPQI) which is a toxic byproduct. Majority is metabolized in the liver via glucuronidation and sulfation (63 and 34%, respectively) and the resulting water soluble metabolites are then excreted in urine. At therapeutic doses, the small amount of NAPQI made by CYP-450 system is conjugated with glutathione in the liver and then excreted as mercaptopuric acid.

When large doses of acetaminophen are ingested, glutathione and sulphate are depleted, causing more of the drug to be shunted to the CYP-450 system. *High concentrations of NAPQI are produced, and in the absence of conjugation with glutathione bind covalently to sulfhydryl groups on proteins, resulting in hepatocellular injury*.

CASE 3: REYE'S SYNDROME

A 3-year-old child CD, suffering from fever, headache and influenza like symptoms was administered aspirin at home by her mother. Later she was admitted to the hospital with altered mental status. Investigations suggest elevated liver enzymes,

hyperammonemia, elevated creatinine and hypoglycaemia. Liver biopsy showed microvesicular steatosis.

CD was diagnosed with 'Reye's syndrome' and necessary treatment was initiated.

The patient gradually recovered and was discharged in two weeks.

Qa. What is 'Reye's syndrome'? What is the possible etiologic agent for 'Reye's syndrome in case of 'CD'? How can Reye's syndrome be avoided?

The Centre for Disease Control and Prevention defines Reye's syndrome as "an acute, non-inflammatory encephalopathy characterized by alteration in the levels of consciousness. The encephalopathy must be associated with either fatty changes of the liver or at least 3-fold increase in the level of ALT, AST, or serum ammonia with no other reasonable explanation for the hepatic and cerebral abnormalities."

Aspirin intake during viral illness in young children may lead to Reye's syndrome characterized by liver failure and encephalopathy.

Aspirin should not be prescribed in fever of unknown origin to children below 12 years. Paracetamol may be used as an antipyretic agent in children.

CASE 4: DRUG THERAPY OF POST-HERPETIC NEURALGIA

A 65-year-old male EF had painful rash on one side in the lower abdomen below the umbilicus. The rash was accompanied with fever, headache and malaise. He was treated with acyclovir 400 mg orally once daily. The rash subsided in 2 weeks but the pain has been persisting for last few months. The pain is described as burning sensation on the skin even from the slightest pressure or rubbed against clothing or temperature changes. It is localised to the region of rash. EF is a known case of diabetes and also a patient of benign hyperplasia of prostate.

The clinical presentation is characteristic of post-herpetic neuralgia which is a type of neuropathic pain.

Qa. What are the treatment options available for 'EF', a case of post-herpetic neuralgia?

The American Academy of Neurology treatment guidelines published in 2004 stated that *tricyclic antidepressants (amitriptyline, nortriptyline and desipramine), gabapentin, pregabalin, opioids and lidocaine patches* are effective and can be used for the treatment of neuropathic pain. Studies have shown that dual norepinephrine/serotonin reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine are also effective in the management of neuropathic pain while selective serotonin reuptake inhibitors (SSRIs) have limited analgesic efficacy.

Qb. How does the opiate system and monoaminergic descending pathways contribute to pain inhibition at the spinal level?

The *endogenous opioid system* consisting of neurons that produce endorphin, enkephalins and dynorphins cause antinociceptive effect by acting at three major classes of receptors, mu, delta, and kappa.

Descending pain inhibitory pathway consists of neurons from the periaqueductal gray (PAG) matter in the upper brainstem, the locus ceruleus (LC), the nucleus raphe magnus (NRM). This pathway involves monoamines such as noradrenaline (NA) and serotonin (5-HT). The serotonergic and noradrenergic systems through 5-HT and α-receptor-mediated actions play a role in the descending inhibitory control of pain.

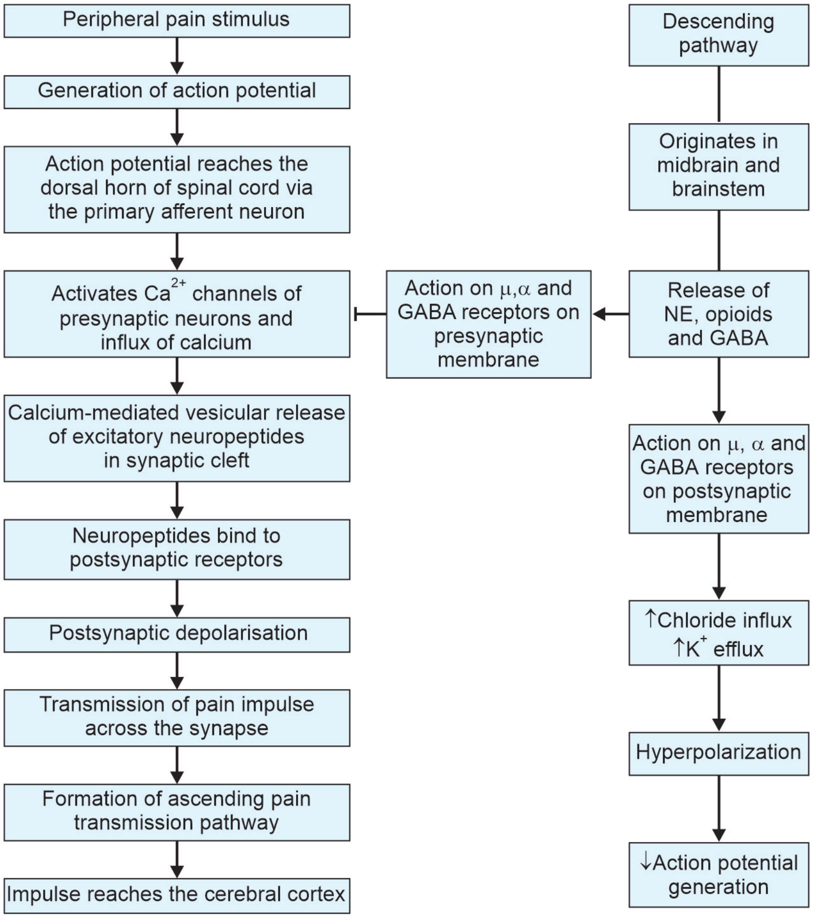

Peripheral pain stimulus
Generation of action potential
Action potential reaches the dorsal horn of spinal cord via the primary afferent neuron
Activates Ca^{2+} channels of presynaptic neurons and influx of calcium
Calcium-mediated vesicular release of excitatory neuropeptides in synaptic cleft
Neuropeptides bind to postsynaptic receptors
Postsynaptic depolarisation
Transmission of pain impulse across the synapse
Formation of ascending pain transmission pathway
Impulse reaches the cerebral cortex
Descending pathway
Originates in midbrain and brainstem
Release of NE, opioids and GABA
Action on μ,α and GABA receptors on presynaptic membrane
Action on μ, α and GABA receptors on postsynaptic membrane
↑Chloride influx
↑K^+ efflux
Hyperpolarization
↓Action potential generation

Fig. 27.2: Involvement of opioid and monoaminergic pathways in pain inhibition at the dorsal horn of spinal cord

At the cellular level in the dorsal horn of the spinal cord, opioid peptides and monoamines act on their respective receptors and modulate nociceptive input in two ways:

1. Action on presynaptic receptors of the primary afferent neuron block calcium-mediated release of neuropeptides and neurotransmitters such as substance P, CGRP and glutamate, responsible for nociception and
2. Action on receptors at the postsynaptic membrane of secondary relay neuron open potassium channels causing K^+ efflux and hyperpolarization of postsynaptic neuron inhibiting the transmission of pain impulse in the secondary relay neuron.

Case Continued

EF was prescribed pregabalin 300 mg daily for controlling his pain.

Qa. How do the antidepressants act in the management of neuropathic pain?

Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline and desipramine and dual serotonin norepinephrine reuptake inhibitors (SNRI) such as venlafaxine and duloxetine produce analgesia by *increasing the activity of descending pain inhibitory pathway* which consists of noradrenergic and serotonergic projections from the brain to the spinal cord. Increased synaptic levels of serotonin and norepinephrine inhibit the nociceptive pathway.

Norepinephrine stimulates α2-adrenergic receptors, expressed presynaptically to inhibit the synaptic release of excitatory neuropeptides and acts postsynaptically to open up K^+ channels causing potassium efflux and subsequent hyperpolarisation, decreasing the nociceptive impulse generation. Selective serotonin reuptake inhibitors (SSRIs) have minimal analgesic action by themselves.

Qb. Given that EF is a 65-year-old elderly male, why do you think TCAs are not appropriate for the treatment of post-herpetic neuralgia?

Tricyclic antidepressants (TCAs) are associated with classic side effects as a result of histaminergic, cholinergic, alpha-adrenergic receptor antagonism and sodium channel blockade. Side effects include dry mouth, constipation, urinary retention, drowsiness, orthostatic hypotension and increased risk of cardiovascular events. Anticholinergic effect could lead to worsening of urinary tract symptoms of benign hyperplasia of prostate. Therefore, the use of TCAs should be carefully monitored in elderly patients with BHP, cardiovascular disease or autonomic neuropathy. Secondary amines such as desipramine and nortryptiline are less anticholinergic, usually better tolerated than the tertiary amines and may be more desirable in the elderly.

Qc. Although both pregabalin and gabapentin are effective in the management of neuropathic pain, why do the clinicians prefer the use of pregabalin over gabapentin?

Gabapentin and pregabalin bind to α2-delta-subunit of voltage-gated calcium channel and prevent the expression of calcium channels on membrane, calcium conduction is blocked and mediators of pain such as substance P, CGRP and glutamate cannot be released from primary afferent neuron leading to antinociceptive action.

Gabapentin is associated with central nervous system adverse effects particularly dizziness, somnolence, confusion and ataxia. Pregabalin has analgesic efficacy and adverse effect profile similar to gabapentin but pregabalin has an advantage that it is more potent and hence dose-related adverse effects are less compared to gabapentin. Hence, pregabalin use is preferred to gabapentin in the management of neuropathic pain.

CASE 5: DRUG THERAPY OF TRIGEMINAL NEURALGIA

A 48-year-old female LM, arrived at the clinic with history of pain on the right side of the face for past 3–4 weeks. The pain was described as severe, unbearable, intermittent, electrical shock like, aggravated while talking, eating, swallowing, washing her face or even touching the face. The dentist could find no problem with her teeth or jaw and over the counter pain relievers provided no benefit. She was treated with carbamazepine 100 mg twice daily and she was relieved of her symptoms.

Qa. How does carbamazepine work in the treatment of trigeminal neuralgia?

Carbamazepine acts by inhibiting voltage-gated sodium channels, thereby suppressing the action potential generation and propagation and subsequently reducing the excitability of neural membranes. It has also been shown to potentiate GABA receptors. This may be relevant to its efficacy in neuropathic pain.

Qb. Why carbamazepine should be used with caution in elderly for the management of neuropathic pain? What precautions can be taken to prevent carbamazepine-related side effects?

Common side effects with carbamazepine include sedation, dizziness, nausea, vomiting, diplopia, memory problems, ataxia, elevation of hepatic enzymes, and hyponatremia, which may contraindicate it for elderly patients. Potentially serious but uncommon side effects are haematological side effects such as leucopenia and aplastic anaemia, hepatotoxicity and Stevens-Johnson syndrome (SJS).

It is advisable to order complete blood count, serum sodium and liver function tests within several weeks after starting therapy to detect any complications. Oxcarbazepine, a keto derivative of carbamazepine that does not pass through the liver cytochrome system, has an improved side effect profile and fewer drug interactions than carbamazepine.

CASE 6: DRUG THERAPY FOR CANCER PAIN

A 55-year-old patient PQ, was diagnosed with stage IV urinary bladder cancer. PET scan showed bone metastasis. She reported severe pain in the lower abdomen and over the lumbar region. His cancer was medically managed with chemotherapeutic agents. For pain relief, he received oral morphine sulphate tablets 10 mg, 4 hourly.

Qa. What are the common concerns associated with acute treatment of pain with morphine? What should be the line of action to manage morphine-induced side effects?

The most common adverse effects of opioids upon initiation of treatment include drowsiness, confusion (delirium), unsteadiness, nausea and vomiting, constipation, sweating, dry mouth or urinary retention. Most of these side effects *with the exception of constipation* subside with time due to tolerance developing in 3–7 days. If the side effects do not diminish with time, treatment may include switching to a different opioid or adding another medication to counteract the undesired effect.

Qb. Constipation is troublesome for the patient PQ. How does morphine induce constipation? What should be the line of action to prevent constipation?

Morphine causes constipation by decreasing propulsive intestinal activity and increasing non-propulsive ring contractions, and by enhancing the absorption of fluid and electrolytes. Patients do not develop tolerance to constipation and require treatment with laxatives. Colonic contact (stimulant) laxatives such as senna and bisacodyl reduce ring contractions in the colon and thereby facilitate propulsive activity.

Qc. Is postural hypotension a problem with morphine?

Morphine can cause histamine release and consequent vasodilation and hypotension. Patients over 70-years-old may experience dizziness or feel unsteady for a few days, but they are asked to continue with the treatment.

Qd. Which opioids can be used as alternative drugs to morphine (opioid rotation) in the management of cancer pain to improve clinical outcome?

Oxycodone, **hydrocodone,** the semisynthetic compounds, are more effective analogues of codeine that are readily available and are widely used, often in combination with acetaminophen.

Methadone is an inexpensive synthetic opioid agonist, has a long half-life, no active metabolites, little tendency to induce tolerance in patients and an effective alternative to treat cancer pain.

Methadone has unique properties that make it useful for treating pain which is poorly controlled by other opioids. In addition to binding opioid μ-receptor, it produces analgesic effects through its *antagonism at the NMDA receptor* site and by *increasing the availability of neurotransmitters serotonin and norepinephrine* within the central nervous system.

Methadone is available for oral, sublingual, rectal intravenous and subcutaneous administration, and has relatively low risk for opioid-associated adverse effects.

Buprenorphine is a potent partial μ-agonist that has been shown to be effective in reversing the effects of full μ-agonists. It is available as an injectable formulation and as tablets for sublingual administration. Buprenorphine has the advantage of having *a prolonged duration of action*.

Tramadol is a centrally acting non-opiate analgesic with low affinity for μ-opioid receptors and is effective in the treatment of moderate-to-severe pain. It has been also shown to inhibit reuptake of serotonin and norepinephrine, which synergistically enhances its weak opioid mechanism of action. The weak action on μ-opioid receptors explains the reduced incidences of abuse, respiratory depression and other adverse effects of traditional opioids in patients on long-term tramadol therapy. Therefore, tramadol may be used in the management of chronic cancer pain.

Qe. What is the rationale for using a combination of acetaminophen/oxycodone in treating PQ's cancer pain?

Acetaminophen is considered to be an effective and the safest analgesic. But the use of acetaminophen alone is not sufficient to control cancer pain. Opioids are typically the most common drug class used in the treatment of cancer pain.

Oxycodone, a semisynthetic derivative of opioid is more effective analogue of codeine. Like other opioids, including morphine, the analgesic effect of oxycodone is mainly mediated through the activation of the μ-opioid receptor.

The predominant mechanisms of acetaminophen's analgesic effects involve the central nervous system (CNS). Acetaminophen and oxycodone acting through different mechanisms exert synergistic or additive effects and improve clinical outcome by enhancing efficacy and reducing the dose-related side effects.

Qf. Why is pethidine (meperidine) not commonly used for long-term pain relief in cancer?

The main metabolite of pethidine is norpethidine which can cause tremor, twitching, agitation and even seizures. Since norpethidine is eliminated by the kidney, toxic manifestations occur with lower doses in patients with poor renal function. Therefore, long term use of pethidine for cancer pain relief is not preferred.

Qg. What is the rationale for morphine use in acute heart failure?

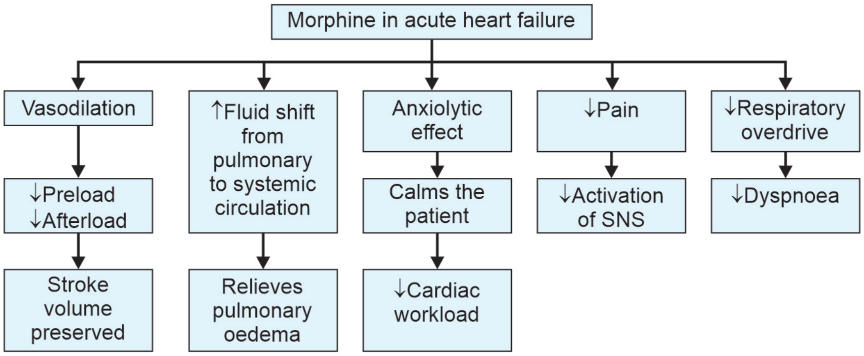

Morphine in acute heart failure
Vasodilation
↓Preload
↓Afterload
Stroke volume preserved
↑Fluid shift from pulmonary to systemic circulation
Relieves pulmonary oedema
Anxiolytic effect
Calms the patient
↓Cardiac workload
↓Pain
↓Activation of SNS
↓Respiratory overdrive
↓Dyspnoea

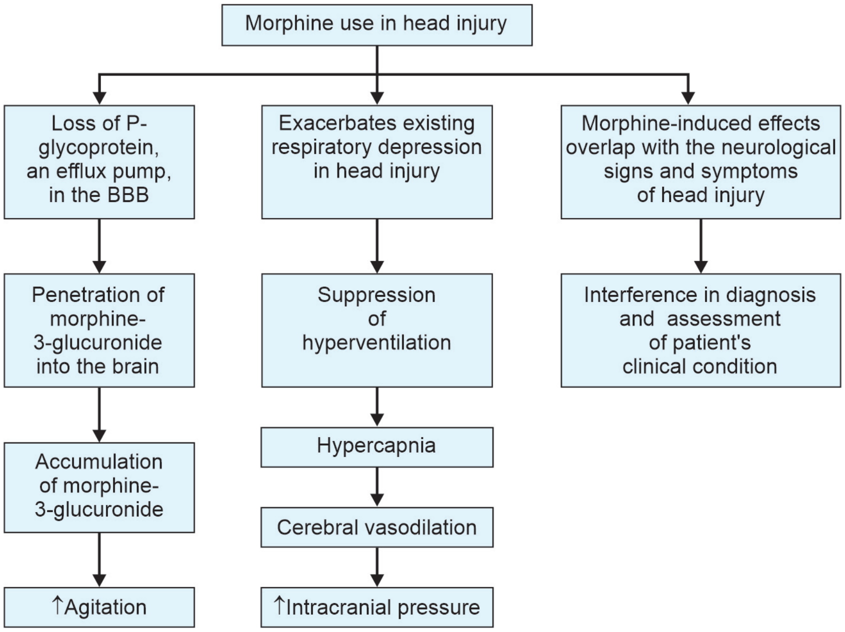
Fig. 27.3: Beneficial effects of morphine in acute heart failure

Morphine is useful in heart failure because of the following reasons:

1. The hemodynamic effects of morphine are due to reduction in venous tone with pooling of blood in the venous circulation. This reduces the venous return and preload to the right ventricle decreasing the end-diastolic pressure, thereby allowing the left ventricle to operate at a lower filling pressure. There is also lowering of cardiac output but the negative effects on cardiac output can be mitigated by the mild reduction in systemic vascular resistance, resulting in decreased afterload and preserved stroke index.
2. In the setting of pulmonary oedema associated with heart failure, the vasodilation may result in a volume shift from central to peripheral circulation alleviating pulmonary congestion and provide symptomatic relief to the patient.
3. Morphine results in a robust and instantaneous anxiolytic effect by activation of the delta- and µ-opioid receptors in multiple brain regions and calms the patient. It improves dyspnoea by reducing associated anxiety and respiratory overdrive.
4. Morphine is an effective analgesic in treating pain of myocardial infarction. Pain activates the sympathetic nervous system and in turn increases the cardiac workload. Thus, it is beneficial in myocardial infarction-associated heart failure by reducing pain and workload on the heart.

Qh. Why is morphine not used in head injury?

During severe brain trauma, the ensuing inflammatory response in the central nervous system results in a decrease in the expression of the transporter protein, *p*-glycoprotein (PGP), in the blood–brain barrier. This loss results in the penetration into the brain of certain drugs that are normally extruded by the transporter protein. The accumulation of morphine-3-glucuronide, a metabolite of morphine, in the brain, is responsible for increasing agitation and may precipitate seizures.



Morphine use in head injury
Loss of P-glycoprotein, an efflux pump, in the BBB
Exacerbates existing respiratory depression in head injury
Morphine-induced effects overlap with the neurological signs and symptoms of head injury
Penetration of morphine-3-glucuronide into the brain
Suppression of hyperventilation
Interference in diagnosis and assessment of patient's clinical condition
Accumulation of morphine-3-glucuronide
Hypercapnia
Cerebral vasodilation
↑Agitation
↑Intracranial pressure

Fig. 27.4: Effects of morphine use in head injury

Morphine acts on µ-opioid receptors in the central nervous system, consequently aggravates the respiratory depression in head injury and depresses the underlying respiratory drive by blunting the body's response to increasing carbon dioxide levels. This results in retention of carbon dioxide in blood causing cerebral vasodilation and raised intracranial pressure.

Morphine may also obscure the clinical course in a patient with a head injury by exhibiting clinical effects (nausea, vomiting, confusion and pinpoint pupil) similar to the neurological signs and symptoms of head injury.

CASE 7: ACUTE MORPHINE POISONING

PQ was under depression for last one year. One day, he was brought to the hospital with decreased levels of consciousness. She was drowsy, difficult to arouse, not responding to verbal stimuli. There was history of consumption of excess morphine tablets. Physical examination revealed pinpoint pupil. The respiratory rate was 9 breaths/min. The patient had a systolic blood pressure of 100 mmHg and diastolic blood pressure of 70 mmHg. Oxygen saturation was 89% on room air.

PQ was diagnosed as a case of 'acute morphine poisoning'.

Treatment advised: **After repeated doses of naloxone (initially, at 6 µg/kg/hour and then increased to 12 µg/kg/hour), she recovered consciousness with no recurrence of symptoms. There was an increase in respiratory rate and volume accompanied by a rise in systolic blood pressure and dilatation of the pupils.**

Qa. Describe the clinical presentation of acute morphine overdosage. Identify the clinical signs and symptoms in PQ, that indicate morphine overdosage.

Acute overdosage with morphine sulphate can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupil and in some cases pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction and death.

The patient PQ characteristically presents with CNS depression, respiratory depression and constricted pupil. The fall in oxygen saturation, respiratory rate and blood pressure indicates respiratory and cardiovascular depression. There is excessive drowsiness which may progress to coma.

Qb. For some alkaloid poisoning such as morphine, gastric lavage is done by adding potassium permanganate. How is this useful? Is gastric lavage necessary in intravenous morphine overdose? Explain.

Potassium permanganate added during gastric lavage, oxidizes alkaloids and converts them into non-toxic compounds.

Morphine injected intravenously, is metabolised in the liver by conjugation. The conjugated metabolites are excreted in bile, which reach the intestine via enterohepatic circulation, subsequently there is reflux of duodenal contents back into the stomach that can result in the deposition of morphine in gastric contents. Therefore, gastric lavage is beneficial in morphine overdose injected intravenously.

Qc. How does naloxone act? Why repeated doses of naloxone are administered in the treatment of morphine poisoning instead of single dose?

Naloxone hydrochloride is a pure opiate antagonist. It is thought to act as a competitive antagonist at µ, kappa and delta opiate receptors although it has highest affinity for µ-receptors. In patients, who have received large doses of morphine, naloxone antagonizes most of the effects of the opiate. There is an increase in respiratory rate and minute volume, arterial PCO2 decreases towards normal, and blood pressure returns to normal if depressed.

Naloxone has a fast onset of action and short half-life of 1 to 2 hours with a short duration of action, while the duration of action of morphine is long. So, naloxone is administered in repeated doses, at short time intervals to ensure continuous action of naloxone on the opioid receptors, until all the morphine is cleared from the body so that relapse does not occur and the desired parameters become normal.

With a single dose of naloxone, the recovery of the patient may be immediate but he may once again advance into respiratory depression and coma. Because the duration of action of naloxone is shorter than that of the opiates, the effects of opiate may return as the effects of naloxone dissipate.

Qd. Opioid-dependent patients treated with naloxone should be closely monitored. Explain with reasons.

In patients who are dependent on opiates, parenteral administration of naloxone hydrochloride will precipitate opiate withdrawal symptoms, which may appear within minutes of naloxone administration and subside in about 2 hours. The severity and duration of the withdrawal symptoms are related to the dose of naloxone and the degree and type of opiate dependence.

CASE 8: FENTANYL USE IN CHRONIC CANCER PAIN

MN, a 77-year-old female patient of chronic pain condition, was found dead due to the application of heating pad over the fentanyl patch attached to the body.

Qa. What type of formulation of fentanyl was applied in case MN? What are the advantages of this formulation?

Fentanyl is available in parenteral, transmucosal and transdermal formulations. It is most widely used in palliative medicine in the form of a transdermal patch as in case of MN.

Transdermal fentanyl is especially useful in those patients who do not have enteral access for analgesia or for whom nausea and vomiting limit the ingestion of required dose of opioid. Transdermal route eliminates gastrointestinal absorption and subsequently first pass metabolism of fentanyl, which makes possible to use lower doses of medication and reduce incidence of adverse effects.

Qb. What is the possible reason for death of the lady MN, treated with fentanyl patches? What caution needs to be taken when using fentanyl patch for the management of chronic pain?

Fentanyl is quick-acting lipophilic opiate, 70 to 100 times more potent than IV morphine. High temperature enhances cutaneous absorption of fentanyl leading to toxicity. Increased levels of fentanyl, can cause serious respiratory depression, impaired consciousness, coma or death.

The patient should be cautioned about avoiding external heating sources such as electric blankets, heating pads, tanning beds, sunbathing, hot baths, hot tubs, saunas, and heated water beds. Fentanyl transdermal skin patches should not be used if skin is damaged or cut because this may increase the absorption of the medication.

CASE 9: PENTAZOCINE USE IN MANAGEMENT OF POSTOPERATIVE PAIN

A 50-year-old male patient XY with history of gallstones, underwent laparoscopic cholecystectomy. He received intravenous 0.5 mg/kg pentazocine, 10 min before surgery to reduce intraoperative hemodynamic changes and postoperative pain.

Qa. How does pentazocine act to relieve pain? What are the advantages of pentazocine use in the management of postoperative pain?

Pentazocine is a synthetic opioid that is a partial agonist at μ-receptors as well as has agonistic action at the peripherally restricted kappa receptors located on visceral and somatic afferent nerves for relief of inflammatory, visceral, and neuropathic chronic pain.

The advantage of pentazocine is that it does not produce tolerance or dependence. It is associated with little or no abuse potential. Higher doses of pentazocine elicit psychotomimetic and dysphoric effects. This may be due to the activation of *supraspinal kappa receptors*. This manifests as anxiety, strange thoughts, nightmares and hallucinations. Therefore, abuse potential is low. It is associated with lower side effect burden than other μ-opioid receptor agonists. Sedation and respiratory disturbances are mild compared to morphine.

Qb. Why is it important to rule out cardiac disease prior to administering pentazocine? Can pentazocine be used in epilepsy or head injury?

Pentazocine is known to cause sympathetic stimulation and rise in catecholamine concentrations, which increases heart rate and blood pressure. In patients with acute myocardial infarction, pentazocine produces substantial elevation in cardiac preload and afterload and thereby increases the cardiac workload. In addition, a decrease in left ventricular ejection fraction due to an increase in systemic vascular resistance is seen.

It is contraindicated in epileptic seizures as it lowers seizure threshold, thus raising the chances of seizures. It is known to increase intracranial pressure so caution should be considered in head injury.

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Chapter

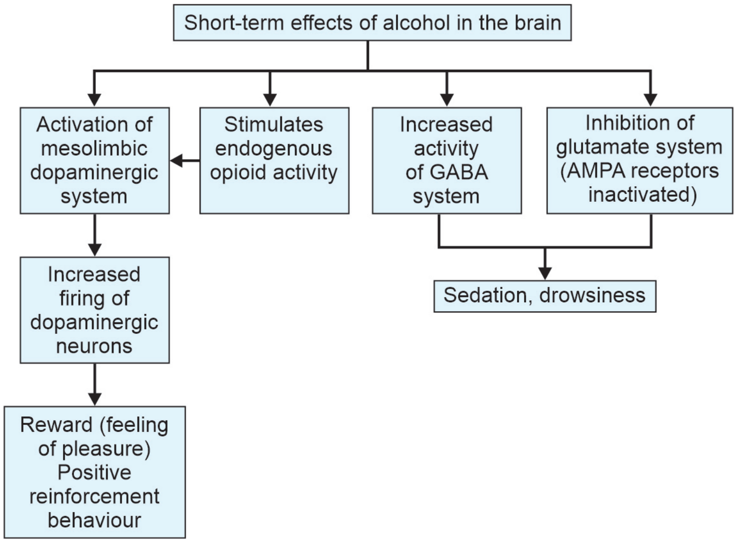
28

Drugs of Abuse

CASE 1: DRUG THERAPY OF ALCOHOL ABUSE AND ALCOHOLISM

Mr AB, 32-year-old male in a corporate job, occasionally drinks with his friends when he attends parties. He enjoys drinking as it makes him happier and helps him to forget his worries. While returning, he avoids driving home as he is drowsy and unstable.

Qa. What do think is the underlying reason for pleasure and reward experienced by Mr AB on drinking alcohol? Explain the mechanisms responsible for sedation and drowsiness.



Short-term effects of alcohol in the brain
Activation of mesolimbic dopaminergic system
Stimulates endogenous opioid activity
Increased activity of GABA system
Inhibition of glutamate system (AMPA receptors inactivated)
Increased firing of dopaminergic neurons
Sedation, drowsiness
Reward (feeling of pleasure) Positive reinforcement behaviour

Fig. 28.1: Short-term effects of alcohol in the brain

Alcohol activates the *mesolimbic dopamine system* which comprises of dopaminergic neurons from the VTA to nucleus accumbens resulting in firing of dopaminergic neurons and increased release of dopamine which is responsible for pleasure and reward.

Alcohol administration enhances endogenous opioid activity which induces dopamine release and produce reinforcement. Serotonin levels in the brain are also boosted which elevate mood. This causes an individual to consume more alcohol and drink more frequently in an attempt to increase 'feel good feelings' that dopamine produces. This positive reinforcement phenomenon subsequently causes addiction or dependence to alcohol.

Ethanol acts as a central nervous system depressant in the following ways:

- It enhances inhibitory neurotransmission by *acting through* $GABA_A$*-receptor*-mediated chloride influx leading to hyperpolarization and inhibition of neuronal activity, causing feelings of calmness and sedation.
- In addition, it decreases excitatory neurotransmission due to the *action on glutamate receptors* resulting in memory loss and other impaired brain functions.

Case Continued

Over a period of years, he has become a hard drinker. His performance at work has declined and he remains absent from work on several days. His wife tries to control him from drinking alcohol because of which there are frequent fights and tension in married life. He wishes to abstain himself from alcohol but fails to do so because he develops tremor, headache, sweating and palpitation. This leads him to quick return to drinking and binge drinking.

Qa. What is dependence?

American Psychiatric Association (APA) in a volume entitled DSM IV defines substance dependence (addiction) as "a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more)" characteristics including tolerance, withdrawal, and giving up or reducing "important social, occupational, or recreational activities because of substance abuse" over a 12-month period.

Qb. How does dependence manifest clinically in an alcoholic patient as in AB?

Physical dependence manifests clinically as *withdrawal symptoms* in the absence of the drug. In case 'AB', it was seen that the initial effects of alcohol is to suppress brain functions resulting in sedation, drowsiness and unsteady gait. But when alcohol is abruptly reduced or discontinued, a withdrawal syndrome may follow, characterized by seizures, tremor, hallucinations, insomnia, agitation and confusion. Thus, the withdrawal symptoms are opposite to the effects of alcohol.

Psychological dependence occurs when alcohol stimulates the reward system of the brain producing pleasure and an urge to continue taking alcohol (positive reinforcement). If alcohol is withheld, the adaptations in reward pathway manifests as dysphoria and craving for alcohol.

Qc. How does alcohol interact with neurotransmitters of the brain to cause dependence and relapse in drinking behaviour using a schematic diagram?

Chronic alcohol consumption induces long-term adaptive and pathological changes in the brain and produces effects opposite to that of short-term alcohol consumption.

1. Effect on mesolimbic dopamine system:

Sustained activation of mesolimbic dopamine system decreases dopamine release by the dopaminergic neurons of the VTA.

2. Effect on GABA system:

Stimulation of $GABA_A$-receptors for prolonged period causes desensitization or downregulation of receptors, decreased $GABA_A$-receptor function, leading to decreased inhibitory neurotransmission.

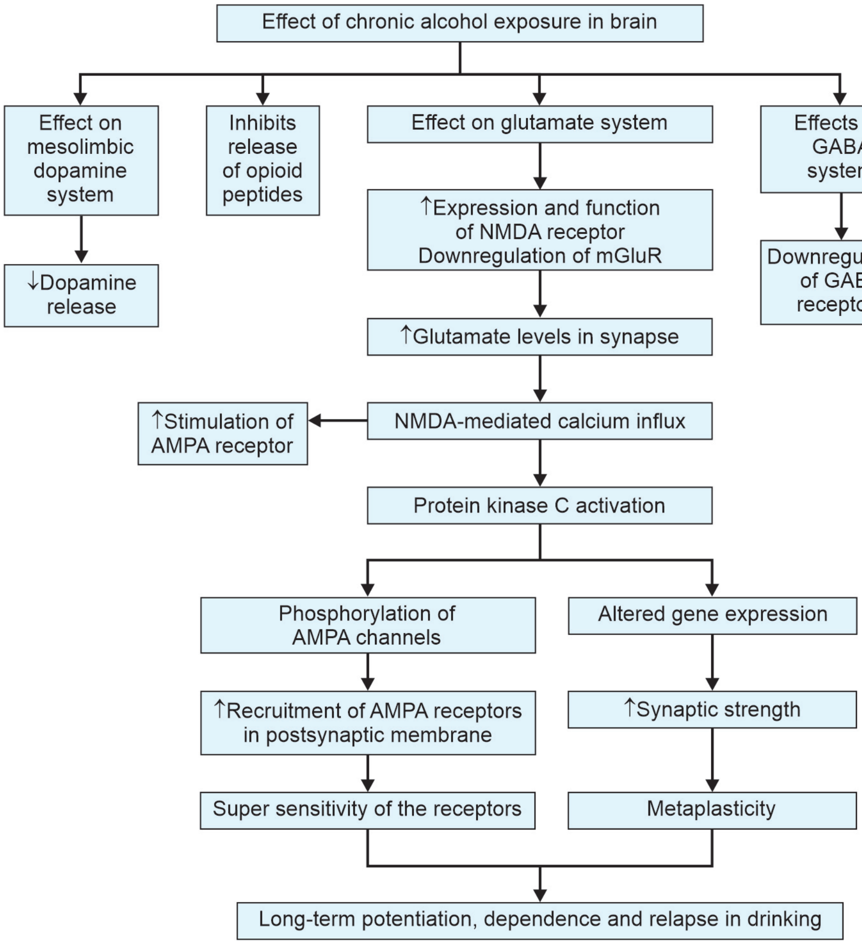

Effect of chronic alcohol exposure in brain
Effect on mesolimbic dopamine system
Inhibits release of opioid peptides
Effect on glutamate system
Effects on GABA system
↓Dopamine release
↑Expression and function of NMDA receptor Downregulation of mGluR
Downregulation of GABA receptors
↑Glutamate levels in synapse
↑Stimulation of AMPA receptor
NMDA-mediated calcium influx
Protein kinase C activation
Phosphorylation of AMPA channels
Altered gene expression
↑Recruitment of AMPA receptors in postsynaptic membrane
↑Synaptic strength
Super sensitivity of the receptors
Metaplasticity
Long-term potentiation, dependence and relapse in drinking

Fig. 28.2: Effect of chronic alcohol exposure in brain

3. Effect on glutamate system:

- The glutamate receptors adapt to the inhibitory effects of alcohol by increasing their excitatory activity. NMDA and metabotropic glutamate receptors play a central role in mediating pathological changes in the brain.
- Prolonged alcohol stimulation causes downregulation of presynaptic mGluR which controls the release of neurotransmitter. This results in increased glutamate levels in the synapse and enhanced activation of AMPA receptors.
- Excess stimulation of AMPA receptors leads to increased expression and function of NMDA receptors in the neuronal cells of the cortex and cerebellum which significantly increases the amount of calcium that enters nerve cells.
- Excess calcium activates protein kinases and phospholipases which cause phosphorylation of AMPA receptors and increase their responsiveness to glutamate. Later, more AMP receptors are recruited to the postsynaptic membrane. Various other mediators and signalling pathways are activated causing structural changes and lead to permanent increase in synaptic contact that in turn leads to metaplasticity and long-term potentiation. Long-term potentiation is long-lasting enhancement of synaptic transmission that occurs at various CNS synapses following a short burst of high frequency presynaptic stimulation.

4. Effect on opioid peptides:

Chronic alcohol abuse leads to reduced brain levels of endorphin which contributes to the negative emotional states that accompany alcoholic withdrawal.

Qd. Mr AB was referred to rehabilitation centre for alcohol addiction treatment. Mention the drugs that are used in addiction treatment of alcohol. How do medications for alcohol addiction treatment work?

Drugs that work for alcohol addiction treatment are as given below:

i. Disulfiram:

- The most common pathway of alcohol metabolism is the oxidation of alcohol through alcohol dehydrogenase to acetaldehyde and conversion of acetaldehyde to acetate by aldehyde dehydrogenase enzyme.
- Disulfiram is an irreversible inhibitor of aldehyde dehydrogenase, leads to the accumulation of acetaldehyde, which is a highly toxic substance responsible for unpleasant symptoms including throbbing headache, facial flushing, nausea, vomiting, orthostatic hypotension, palpitation and respiratory difficulty. Thus, disulfiram administration paired with alcohol causes the aversive reaction.

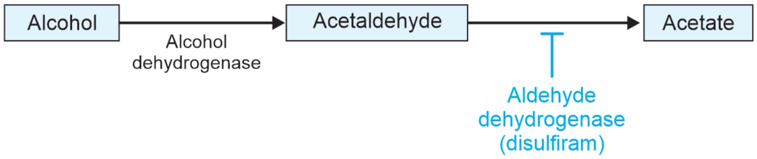


Fig. 28.3: Alcohol metabolism pathway

ii. Naltrexone:

- Opioid peptides (endorphins, enkephalins and dynorphin) activate mesolimbic reward system.
- Naltrexone is a competitive opioid antagonist and can effectively prevent 'high', but it does not alleviate cravings or withdrawal effects. Therefore, naltrexone is effective only in individuals addicted to alcohol who have a high motivation to stay drug free.
- Transient, asymptomatic hepatic transaminase elevations have been observed. Therefore, naltrexone should be used with caution in patients with active liver disease.

iii. Acamprosate:

Inhibits NMDA receptor-mediated calcium influx and stimulates mGluR5 which are downregulated following chronic alcohol consumption. Activation of mGluR5 controls the release of glutamate into the synaptic cleft. Acamprosate reduces symptoms such as insomnia, anxiety and restlessness and is useful in the treatment of alcohol dependence.

iv. Topiramate:

Topiramate has multiple mechanisms of action. It inhibits inotropic glutamate receptors (iGluRs) and can cause activation of GABA receptors. It subsequently attenuates alcohol cravings and consumption.

v. Rimonabant:

Rimonabant is a cannabinoid CB1-receptor antagonist and prevents the actions of endocannabinoids which contribute to the induction of synaptic plasticity during learning and memory function.

CASE 2: DRUG THERAPY FOR NICOTINE ADDICTION

A 22-year-old young male CD, with history of smoking for last 10 years is diagnosed with chronic bronchitis. Currently, he is smoking 2 packs/day. He smokes several cigarettes in succession immediately after waking in the morning. He occasionally drinks alcohol. He has been advised by the clinician to quit smoking and avoid alcohol.

He visited smoking cessation rehabilitation centre and expressed his desire to stop smoking. Out of the various options offered to him he decided to use nicotine transdermal patch as a replacement to tobacco delivered nicotine.

Qa. Why do you think CD smokes several cigarettes in the morning?

In chronic smokers there are adaptations in the reward pathway that lead to positive reinforcement, and addiction. There are feelings of discomfort and craving during abstinence because of reduced levels of dopamine in nucleus accumbens and these feelings reinforce drug (nicotine) seeking behaviour. When Mr CD inhales cigarette smoke, nicotine in the smoke is rapidly absorbed into the blood and starts affecting the brain within seconds and 'CD' experiences a feeling of pleasure and reward.

Qb. What are the effects of tobacco delivered nicotine on neurochemical system that causes feeling of reward and craving for nicotine?

The neurobiological mechanisms underlying nicotine addiction includes the following:

Effect on mesolimbic dopamine system: Nicotine directly stimulates α4β2-nicotinic acetylcholine receptors located in the mesolimbic dopamine system which consists of dopaminergic projections from ventral tegmental area (VTA) to nucleus accumbens (NAc) causing dopamine release and feeling of reward.

Outside the mesolimbic dopamine system, reward pathway is modulated by glutamate system and GABAergic neurotransmission.

Effect on glutamate system: Nicotine activates the nAChR at the glutamatergic terminals releasing excess glutamate which stimulates the NMDA receptors in the VTA resulting in dopaminergic hyperactivity.

Effect on GABA system: It decreases GABA inhibitory acivity on dopaminergic neurons resulting in excess and prolonged firing of dopaminergic neurons.

Qc. The clinician discussed various medications available to aid smoking cessation in CD. How does varenicline act to benefit the patient? What caution needs to be considered while prescribing varenicline to a patient?

Varenicline acts as a *partial agonist at α4β2-nicotinic acetylcholine receptor (nAchR)* which means it binds to the nAchR of the reward pathway preventing the binding of nicotine to the receptor and simultaneously exerting some degree of stimulatory action on nAchR therby maintaining moderate levels of dopamine in the brain. This helps to reduce cravings and withdrawal symptoms while preserving the rewarding effects of smoking.

Varenicline treated patients have increased risk of :

i. Neuropsychiatric adverse events such as depression, agitation/aggression, mood or behaviour changes and seizures.
ii. Cardiovascular events (myocardial infarction, ischemic and hemorrhagic stroke).

Therefore, clinicians should exercise caution and careful monitoring of the patients is required when prescribing varenicline particularly in patients with cardiovascular disease and in smokers with current or past psychiatric disorders.

Qd. How does bupropion work? The clinician advises CD that if he undergoes abrupt discontinuation of alcohol, bupropion use should be avoided. Give reasons.

Bupropion is a norepinephrine/dopamine reuptake inhibitor (NDRI) and increases brain levels of dopamine, noradrenaline and serotonin and thereby result in feelings of reward, reducing craving and withdrawal symptoms that occur with nicotine withdrawal.

Seizures are a dose-related toxicity associated with bupropion therapy. For this reason, bupropion is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines). Bupropion also is contraindicated in patients with anorexia or bulimia nervosa, and patients currently taking monoamine oxidase inhibitors owing to the increased potential for seizures in these populations.

Qe. What are the various forms of nicotine replacement therapy? How do they help in cessation of smoking?

Nicotine replacement products available are nicotine transdermal patch, nicotine gum, nicotine lozenges, nicotine nasal spray and inhaler. They make it easier to abstain from tobacco by partially replacing nicotine. They reduce reinforcing effects of nicotine and withdrawal symptoms arising as a result of smoking cessation and helps to quit smoking.

CASE 3: DRUG TREATMENT FOR OPIOID DEPENDENCE

A 35-year-old man LK, heavy heroin user visited the psychiatry clinic for consultation. There was a history of stopping the drug (heroin) in an attempt to wean himself from it. At the time of presentation his signs and symptoms included watery eyes, stomach cramps, dilated pupils, sweating, chills, increased blood pressure and heart rate. He was also seen to be restless, angry and seeking for a drug or remedy for his state. Mr LK was treated with 20 mg of methadone, a long-acting opioid, after which he felt more comfortable and his symptoms improved and was referred to deaddiction centre for further treatment.

Qa. How do you explain the signs and symptoms experienced by LK who attempts to withdraw himself from heroin, an opioid derivative?

The physical signs and symptoms which include watery eyes, stomach cramps, dilated pupils, sweating, chills, increased blood pressure and heart rate are *withdrawal symptoms* which the patient undergoes when heroin (opioid) is abruptly reduced or discontinued. This suggests *addiction or dependence* to the drug resulting from adaptations that occur at the cellular level due to repeated administration of the drug which are unmasked when opioids are abruptly reduced or discontinued.

Subsequently, there is cellular excitability and enhanced activity of locus ceruleus neurons which releases excessive amount of noradrenaline causing effects which are opposite to the pharmacological actions of opioids (heroin) and is seen in case of Mr LK.

Qb. What are the important pharmacokinetic features of heroin that favour its abuse by drug addicts?

Heroin is relatively *non-polar compound* compared to morphine, has high lipid solubility which facilitates its passage across the blood–brain barrier and causes rapid increase in brain concentrations and produces a sharper 'high'.

Heroin is *fast acting* and is *injected intravenously* causing rapid increase in plasma concentrations, thereby increasing the concentrations in the brain and inducing euphoria.

Qc. Why did Mr LK, over a period of time, finds the effects of heroin less intense than when he first started using it?

Heroin produces euphoria due to activation of dopaminergic reward pathway. With repeated administration of the drug, there are adaptations in the brain reward pathway which reduces VTA's release of dopamine into the nucleus accumbens. This may prevent LK from obtaining pleasure from same dose of opioid (heroin) or require higher dose of opioid (heroin) to obtain the same level of response that was achieved initially. LK gradually develops tolerance to opioid. This promotes drug seeking behaviour and compels the person to use higher doses of opioid (heroin). Eventually, opioid tolerance leads to the development of *addiction or psychological dependence and cravings for the drug.*

Qd. Explain the molecular mechanisms that mediate 'opioid dependence'.

The underlying molecular mechanism of heroin that mediates *physical dependence* is at the level of the cellular target. Short-term administration of heroin (opioid), produces μ-opioid receptor-mediated *inhibition of adenylate cyclase*, decreased cyclic AMP and through a series of events causes *inhibition of cellular activity resulting in the pharmacological actions of opioid.*

Long-term exposure to heroin alters gene transcription. There is *increased synthesis of transcription factor cAMP response element binding protein (CREB)* which restores the levels of adenylate cyclase, so that heroin can no longer cause changes in cell firing. There is inhibition of pharmacological actions of heroin, that is, tolerance to heroin develops which gives rise to *physical dependence or addiction resulting in withdrawal syndrome* on sudden discontinuation of heroin.

Qe. Why was Mr LK, who is addicted to heroin, an opioid derivative treated with methadone, an another opioid?

Although methadone is an opioid, certain pharmacokinetic and pharmacodynamics properties of methadone make it a suitable drug for the treatment of opioid (heroin) addiction.

1. Methadone unlike heroin is *slow-acting*, causes gradual rise in plasma concentration which prevents immediate feeling of 'high'.
2. It has a *long elimination half-life*, maintains steady level in the plasma for 24 hours and reduces cravings for longer period compared to heroin.
3. *There is slow decline in plasma concentration* of methadone and prevents withdrawal symptoms which are more likely with heroin which falls quickly producing withdrawal symptoms.
4. *Oral dosage form* of methadone allows slow uptake into the circulation unlike heroin which is injected intravenously and causes instant euphoria.
5. Methadone is *less lipid soluble* compared to heroin which is highly lipid soluble. Therefore, major portion of the drug is metabolized before reaching the brain.

Qf. What is the role of buprenorphine in the management of opioid addiction? Explain the rationale for combining buprenorphine and naloxone administered as a sublingual tablet.

Buprenorphine is a partial opioid agonist of the μ-receptor and relieves drug cravings while eliminating withdrawal symptoms due to its slow onset and long duration of action.

Buprenorphine is combined with naloxone which is an opioid antagonist and is administered as a sublingual preparation. Buprenorphine is quickly absorbed into the circulation and full effects of buprenorphine are experienced while naloxone is inactivated.

If misused parenterally by the individual, naloxone antagonizes the agonist effects of buprenorphine and rewarding effects of buprenorphine are not felt. This prevents abuse of the medication.

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Chapter

29

Uterine Stimulants (Oxytocics) and Uterine Relaxants (Tocolytics)

CASE 1: OXYTOCIC AGENTS FOR AUGMENTATION OF LABOUR

A 40-year-old gravida III woman, RS, was admitted to the hospital at 39.2 weeks of gestation with complaints of intermittent hypogastric pain and vaginal bleeding. Vital signs are unremarkable. Ultrasonographic imaging shows polyhydramnios. On obstetric examination, the clinician recorded a 33 cm fundal height. The cervix was 2 cm dilated and 60% effaced. Close monitoring of progress of labor reveals sudden decrease in uterine contractions 10 hours later.

It was decided to commence oxytocin to accelerate labor. Oxytocin was constituted by adding 10 IU oxytocin to 1 litre of 0.9% normal saline and started at an infusion rate of 1–5 mU/min and titrated upwards.

Qa. What is meant by 'oxytocic drugs'? Which drugs are categorized as 'oxytocic' or 'uterotonic' drugs?

Oxytocic drugs are those used to stimulate uterine activity. They are also called uterotonic drugs.

Oxytocic or uterotonic drugs are the following:

- Oxytocin
- Ergot derivatives: ergometrine, methylergometrine
- Prostaglandins: PGE2, PGF2α, 15-methyl PGF2α and misoprostol.

Qb. Mention the indications for oxytocic drugs.

Oxytocic drugs are used for several indications in obstetrics. These include:

1. Induction of labor
2. Active management of labor
3. Treatment of labor arrest
4. Treatment of uterine atony and postpartum hemorrhage
5. The contraction stress test to evaluate fetal well-being during the antepartum period.

Qc. Explain why oxytocin is preferred over ergometrine in case of RS to accelerate uterine activity.

Oxytocin is the first-line agent in active management of labor because of the following reasons:

1. Oxytocin simulates normal pattern of uterine contraction during delivery. The fundus and body of the uterus contracts whereas the lower uterine segment does not contract. This helps in the delivery of the fetus.
2. At low dose, there is complete uterine relaxation in between uterine contractions thus reducing the chances of fetal distress.
3. Infusion dose can be easily adjusted.
4. Short half-life ($t_{1/2}$), hence action can be terminated when required.
5. Systemic side effects are less.
6. Fewer drug interactions are noted with oxytocin when compared with other uterotonic agents.

Ergometrine acts directly on myometrium and the uterus goes into a state of spasm. There is simultaneous contraction of upper and lower segment with no relaxation in between contractions. This property of ergometrine is not favourable for fetal descent and enhances the chances of fetal distress.

Qd. What are the risks associated with injudicious use of oxytocin?

1. Fetal hypoxia, particularly if the baby is already growth restricted or the frequency of uterine contractions are excessive.
2. Uterine rupture in multiparous women, particularly if the uterus was previously scarred.
3. Water intoxication associated with maternal and neonatal hyponatremia. This is more likely to occur when high doses of oxytocin have been given with large amounts of electrolyte free fluid.
4. Interaction with inhalation anesthetics such as cyclopropane, enflurane, halothane and isoflurane. Occasionally, this may result in hypotension or cardiac rhythm disturbances.
5. Prostaglandins may potentiate the uterotonic effect of oxytocin and vice versa.

Qe. What measures should be considered to avoid oxytocin-induced side effects?

Oxytocin should be started at low dose, titrated up to optimal response (each contraction for 45 seconds, 3 contractions/10 minutes) and the optimal response dose should be continued. This is known as 'oxytocin titration technique'.

During oxytocin administration, contractile tone, frequency and amplitude should be monitored in conjunction with fetal heart rate. If maternal or fetal distress occurs, contractions are too powerful, or the uterus is too reactive, oxytocin should be immediately discontinued.

Qf. What is the role of prostaglandins in induction of labour? Why do you think oxytocin is preferred over prostaglandins in the induction of labor?

Exogenous prostaglandins, e.g. prostaglandin E2 is effective for both cervical ripening and labor induction. Prostaglandin E2 is typically administered intravaginally for *cervical ripening as the first step in labor induction*. It is administered as gel, tablet or controlled release pessary.

Oxytocin is less effective for labor induction when used in women with uneffaced and undilated cervices. Therefore, ripening process should be used prior to oxytocin induction when the cervix is unfavourable. In case of RS, cervix is dilated and effaced, there is no malpresentation, cephalopelvic disproportion, the fetal condition is good, thus making oxytocin a favourable choice.

Case Continued

The third stage of labor was actively managed and then the perineal laceration was sutured. The patient successfully delivered a healthy female infant of weight 3.5 kilogram by vaginal route. The total amount of blood loss was about 1000 ml. The patient suffered from postpartum haemorrhage (PPH) due to uterine atony. In addition, she was given a dose of 200 mcg methylergometrine by intramuscular injection. After hours of intensive treatment, there was no further bleeding episodes. Uterine atony and a first degree vaginal tear were recorded.

Qa. Compare and contrast between ergot derivatives (ergometrine) and oxytocin.

Comparison between ergot derivatives and oxytocin

Properties	*Ergot alkaloid (ergometrine)*	*Oxytocin*
Mode of action	• Tetanic contractions • Loss of polarity	• Physiological contraction • Polarity maintained
Onset of action	• Slower (1 min)	• Faster (30 sec)
Duration	• Long sustained (3 hrs)	• Short duration (8 min)
Clinical use	• To stop haemorrhage from open uterine sinuses following delivery or abortion • Prophylactic use in late second or third stage of labour, to hasten separation of placenta and to minimize blood loss	• Induction of labour • To accelerate uterine contraction during labour • As an haemostatic in adjunct with ergot derivative or in isolation
Hazards	• Rise in blood pressure • Rarely gangrene of toe • Adverse drug reaction persists for long time due to long $t_{1/2}$	• Uterine rupture • Antidiuretic effect • Anginal pain or shock • Adverse drug reaction terminates within minutes due to very short $t_{1/2}$
Limitations	• Should not be used prophylactically in cardiac disease, severe hypertensive disorder, Rh-negative mother • Not to be used during labour prior to crowning of head	• Should not be used in case of grand multipara, contracted pelvis, post C/S, malpresentation • As an haemostatic-rapid intravenous injection is contraindicated

CASE 2: TOCOLYTIC THERAPY FOR ACUTE PRETERM LABOUR

A 30-year-old, G_5P_2, is admitted to the hospital at 30 weeks' gestation with regular painful uterine contractions. 4 hours later a repeated cervical examination shows her cervix to be 4 cm dilated and 90% effaced. There is a past history of prior spontaneous preterm deliveries at 28–31 weeks' gestation.

You make a diagnosis of preterm labor and consider initiation of tocolytic therapy.

Qa. What is the goal of tocolysis?

The goal of tocolysis is to delay delivery for 48 hours to allow administration of a full course of antenatal corticosteroids and the patient to be transferred to a tertiary care center.

Qb. What tocolytic agents are available? How do these agents act to suppress uterine contractions?

Tocolytic agents that can be used in preterm labour to inhibit contractions of myometrial smooth muscle cells include:

1. Magnesium sulphate
2. Calcium channel blockers: Nifedipine
3. Prostaglandin inhibitors: Indomethacin
4. Oxytocin antagonists: Atosiban
5. β-adrenergic agonists: Terbutaline sulphate, ritodrine hydrochloride
6. Nitric oxide donors

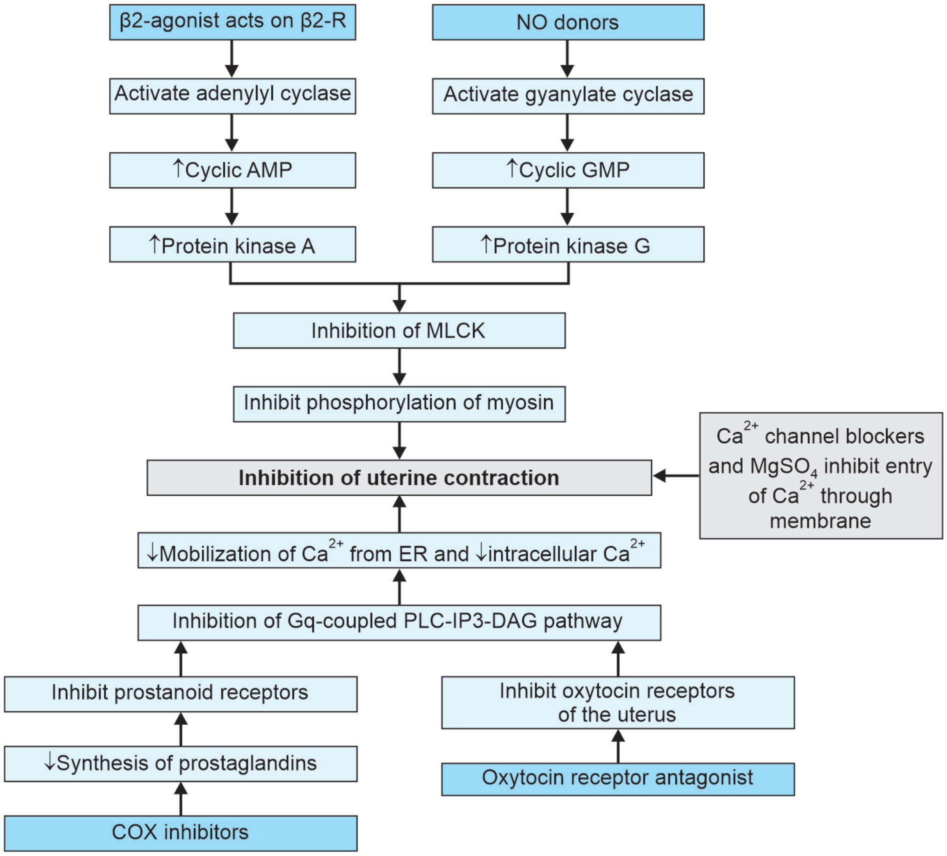

β2-agonist acts on β2-R
Activate adenylyl cyclase
↑Cyclic AMP
↑Protein kinase A
NO donors
Activate gyanylate cyclase
↑Cyclic GMP
↑Protein kinase G
Inhibition of MLCK
Inhibit phosphorylation of myosin
Inhibition of uterine contraction
Ca2+ channel blockers and MgSO4 inhibit entry of Ca2+ through membrane
↓Mobilization of Ca2+ from ER and ↓intracellular Ca2+
Inhibition of Gq-coupled PLC-IP3-DAG pathway
Inhibit prostanoid receptors
↓Synthesis of prostaglandins
COX inhibitors
Inhibit oxytocin receptors of the uterus
Oxytocin receptor antagonist

Fig. 29.1: Tocolytic agents and mechanisms for inhibition of uterine contraction

1. **β2-agonists** interact with β2-receptors of the smooth muscle of uterus with subsequent activation of adenylyl-cyclase-cyclic AMP pathway, increasing the concentration of cyclic AMP, that inhibits myosin light chain kinase (MLCK)-mediated phosphorylation of myosin and uterus contraction.
2. **NO donors** inhibit contraction of uterus through Guanylate-cyclase-cyclic GMP pathway.
3. **Calcium channel blockers and magnesium sulphate** inhibit entry of calcium through the membranes and in turn lessen uterine contractions.
4. **Oxytocin receptor antagonists** inactivate oxytocin receptors.
5. **COX inhibitors** decrease the synthesis of prostaglandins thereby reducing the action on prostanoid receptors.

Oxytocin receptors and prostaglandin (prostanoid) receptors are coupled to Gq-PLC-IP3-DAG pathway. IP3 mobilizes Ca^{2+} from endoplasmic reticulum, increases intracellular Ca^{2+} and enhances contraction of uterus.

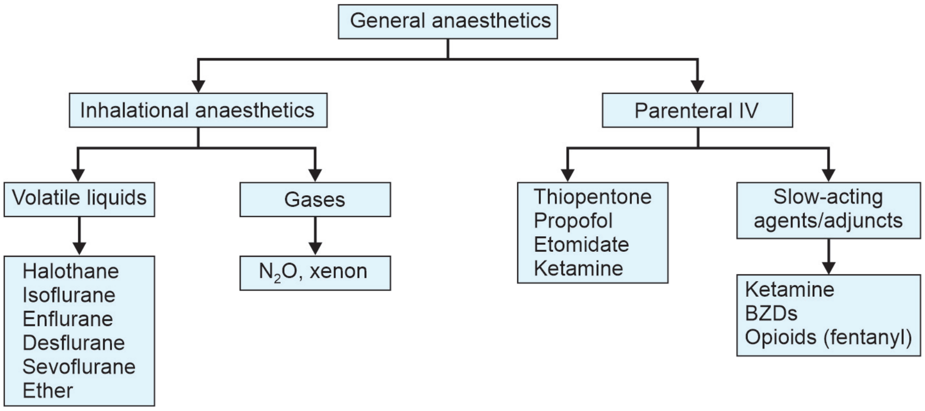
Chapter 30

General Anaesthetics

CASE 1: GENERAL CONSIDERATIONS AND MEDICATIONS USED IN ANAESTHESIA

A 45-year-old male JK, undergoes hip replacement surgery. Prior to surgery, his vital signs are stable with pulse 75/min and blood pressure 120/80 mmHg. JK received atropine 0.5 mg, promethazine and pethidine 1 mg/kg IM 30–45 minutes prior to anaesthesia. The anaesthesiologist rapidly induces anaesthesia with an intravenous bolus of 3 mg/kg of thiopental (a barbiturate). Within 30 seconds, JK is in a deep anaesthetic state.

Qa. How do you classify general anaesthetic agents?



General anaesthetics
Inhalational anaesthetics
Parenteral IV
Volatile liquids
Gases
Halothane
Isoflurane
Enflurane
Desflurane
Sevoflurane
Ether
N_2O, xenon
Thiopentone
Propofol
Etomidate
Ketamine
Slow-acting agents/adjuncts
Ketamine
BZDs
Opioids (fentanyl)

Fig. 30.1: Classification of general anaesthetic agents

Qb. How do the anaesthetic agents used for general anaesthesia act?

The actions of general anaesthetic agents on ion channels of neuronal tissues can influence either the presynaptic release of neurotransmitters, alter the postsynaptic response threshold to neurotransmitters, or both.

They are believed to *inhibit excitatory presynaptic channel activity* mediated by serotonergic, and glutaminergic receptors, while also *augmenting the inhibitory postsynaptic channel activity* mediated by $GABA_A$ and glycine receptors. This reduces neuronal and synaptic transmission. It is possible that modulation of central nicotinic transmission by volatile agents contributes to analgesia. The main effect of anesthetic agents on nicotinic acetylcholine receptors is inhibitory.

Most general anaesthetics (e.g. propofol, etomidate, pentobarbital or halothane) produce anaesthesia by *increasing the activity of inhibitory GABA type A receptors* in the brain. Exceptions to this rule are ketamine, xenon and nitrous oxide that produce anaesthesia by interacting with other brain receptors, mainly, but not exclusively by *inhibiting NMDA brain receptors.*

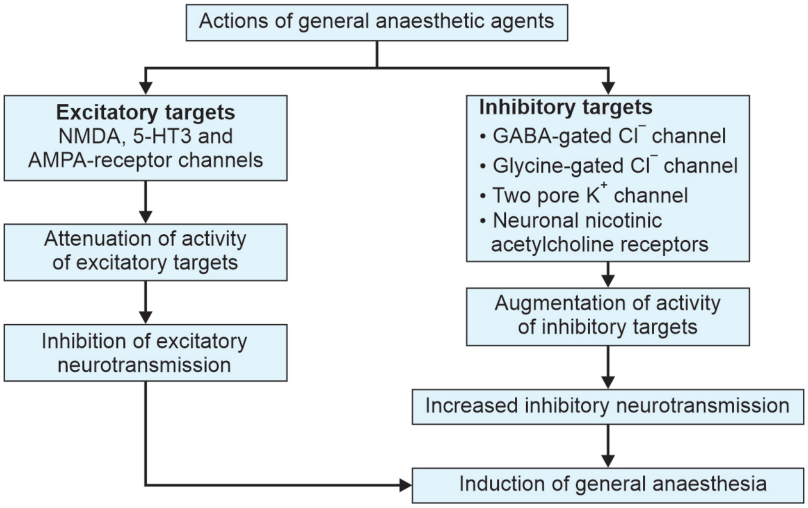

Actions of general anaesthetic agents
Excitatory targets
NMDA, 5-HT3 and AMPA-receptor channels
Attenuation of activity of excitatory targets
Inhibition of excitatory neurotransmission
Inhibitory targets
• GABA-gated Cl$^-$ channel
• Glycine-gated Cl$^-$ channel
• Two pore K$^+$ channel
• Neuronal nicotinic acetylcholine receptors
Augmentation of activity of inhibitory targets
Increased inhibitory neurotransmission
Induction of general anaesthesia

Fig. 30.2: Actions of general anaesthetic agents

Qc. What do you understand by 'induction' and 'maintenance' phase of general anaesthesia?

Induction phase is the transition from awake state to anaesthetized state. It consists of analgesia, loss of memory and the stage ends with loss of consciousness. Inducing agents are fast-acting agents which help to reduce the time spent in stage 2 as much as possible and to facilitate entry to stage 3. Stage 2 is the stage of excitement and delirium, and is undesirable for the patient.

The overall goals of the **maintenance phase** of a general anaesthetic are to maintain stage III surgical anaesthesia (i.e. unconsciousness, amnesia, immobility, unresponsive to surgical stimulation) at a safe anaesthetic depth while also maintaining respiratory and hemodynamic stability.

Qd. Mention commonly used anaesthetic agents for induction and maintenance of general anaesthesia.

Intravenous agents (thiopental, propofol, etomidate and ketamine) are commonly used for induction. Inhaled anaesthetics are preferred for maintenance of anaesthesia.

Qe. In case of XY, which anaesthetic agent is used for induction and maintenance of general anaesthesia?

In case of XY, thiopentone sodium is used as an inducing agent and halothane in combination of O_2 and N_2O is used for maintenance of anaesthesia.

Qf. What accounts for rapid induction and short duration of action of thiopental as an anaesthetic agent?

Thiopental produces rapid and pleasant induction with rapid recovery with no CNS excitation. It has *very high lipid solubility* and hence rapidly crosses the blood–brain barrier and distributed in the CNS and spinal cord, causing unconsciousness within about 20s, lasting for 5–10 min when injected intravenously.

The short duration of action of sodium thiopental is mainly due to *redistribution from its site of action (the highly-perfused brain) into other tissues (e.g. the poorly-perfused adipose tissue,* due to its very high lipid–water partition coefficient (approximately 10). Once redistributed, the free fraction in the blood is metabolized in the liver by zero order kinetics.

Qg. Why is thiopental not used for maintenance of anaesthesia but is only used as an inducing agent?

The recovery of the anaesthetic effect is rapid following a single dose of thiopental given intravenously. The recovery results primarily from *redistribution of thiopental and not rapid metabolic elimination*. Thus, multiple doses for maintenance would result in sequestration of the drug in muscle and adipose tissue followed by its slow release into the circulation and delay recovery.

Thiopental metabolism shows *saturation kinetics*. As more drug accumulates in the body and metabolism saturates, there is slow clearance leading to long half-life and prolonged period of anaesthesia due to the drug. This may cause non-arousable of the individual even after 24 hours.

Qh. Should thiopentone be used as an anaesthetic agent with a previous history of acute intermittent porphyria? Explain with reasons.

Thiopentone (barbiturates) can induce fatal attacks of porphyria in patients with acute intermittent or variegate porphyria and are contraindicated in such patients. Abnormal synthesis of protoporphyrin results in excess porphobilinogen.

Barbiturates induce δ-ALA synthase, an enzyme responsible for porphobilinogen synthesis leading to excessive porphobilinogen levels that can precipitate acute porphyrin crisis. This is manifested by severe abdominal pain, nausea and vomiting, constipation or diarrhea, red or brown urine, tachycardia, neurologic abnormalities and neuropsychiatric disorders.

Qi. What is the risk of inadvertent intra-arterial injection of thiopental sodium (pentothal)?

Thiopental sodium (pentothal) is administered by the *intravenous route*. Accidental intra-arterial injection of thiopental sodium causes severe arterial spasm and an intense burning pain around the injection site. It can induce a severe inflammatory and potentially necrotic reaction that can threaten limb survival.

Qj. How do you explain for shock following rapid administration of anaesthetic agent thiopental, experienced by wounded men who are hypovoleemic?

Thiopental can cause direct myocardial depression and venodilation producing a significant reduction in cardiac output and blood pressure. Thus, thiopental administration, in debilitated and severely ill patients, who are hypovolemic without adequate compensatory mechanisms, may result in severe hemodynamic depression and shock.

Qk. Though ether is a potent anaesthetic and produces good analgesia and marked muscle relaxation, it is not commonly used in developed countries. Explain why.

Ether is a highly volatile liquid, produces irritating vapours which are inflammable and explosive. It is highly soluble in blood. Thus, induction is prolonged and unpleasant with struggling, breath holding, salivation and marked respiratory secretions. So, atropine must be given as premedication to prevent the patient from drowning in his own secretions.

Recovery is slow; postanaesthetic nausea, vomiting and retching are marked. Therefore, it is not preferred in developed countries.

However, it is still used in developing countries, particularly in peripheral areas because it is cheap, can be given by open drop method without the need for any equipment, and is relatively safe even in inexperienced hands.

Case Continued

JK was further intubated on mechanical ventilation. A mixture of inhaled general anaesthetics consisting of halothane in 30% O_2/70% N_2O was provided through ventilation to maintain the anaesthetic state. JK shows no response, either through movement or increased sympathetic tone (e.g. increased heart rate, increased blood pressure) to the first surgical incision. There is loss of corneal reflex and loss of ocular movements.

Qa. Mention the various stages of general anaesthesia.

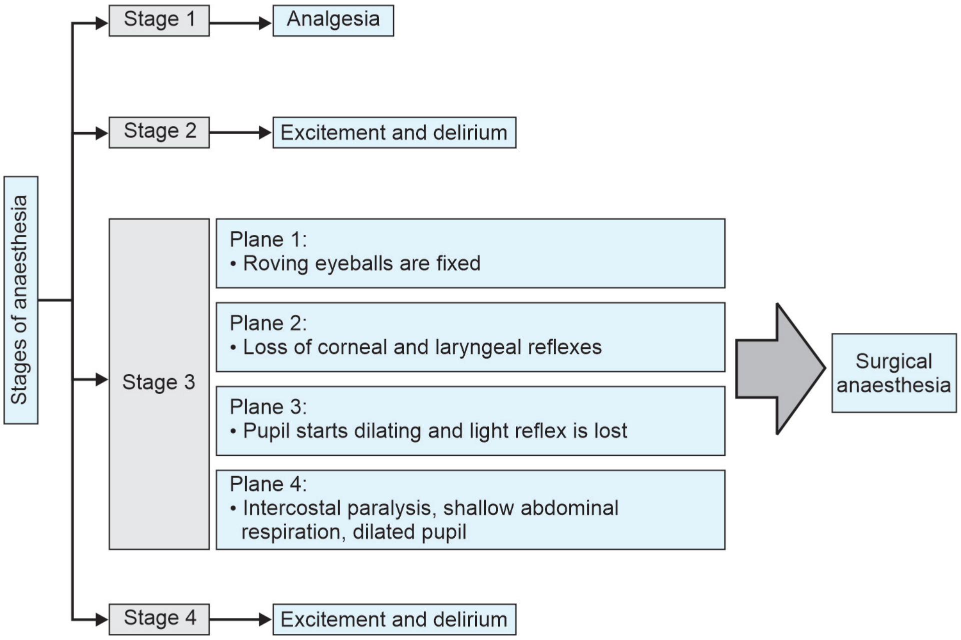

Stages of anaesthesia
Stage 1
Analgesia
Stage 2
Excitement and delirium
Stage 3
Plane 1:
• Roving eyeballs are fixed
Plane 2:
• Loss of corneal and laryngeal reflexes
Plane 3:
• Pupil starts dilating and light reflex is lost
Plane 4:
• Intercostal paralysis, shallow abdominal respiration, dilated pupil
Surgical anaesthesia
Stage 4
Excitement and delirium

Fig. 30.3: Stages and planes of general anaesthesia

Qb. In case of JK, identify the stage of general anaesthesia. What are the components of surgical anaesthesia? What are the advantages of performing a surgical procedure in the stage of 'surgical anaesthesia'?

JK is in stage 3 and plane 2 of general anaesthesia. The stage is known as 'surgical anaesthesia'.

The components of 'surgical anaesthesia' are amnesia, analgesia, unconsciousness, immobility in response to noxious stimulation and attenuation of autonomic responses to noxious stimulation.

The following are the advantages of performing surgery in stage 3, which is the stage of surgical anaesthesia:

1. Minimizing the potentially deleterious direct and indirect effects of anaesthetic agents and techniques.

2. Sustaining physiologic homeostasis during surgical procedures that may involve major blood loss, tissue ischaemia, reperfusion of ischaemic tissue, fluid shifts, exposure to a cold environment, and impaired coagulation.
3. Improving postoperative outcomes by choosing techniques that block or treat components of the surgical stress response that may lead to short- or long-term sequelae.

Qc. What is minimum alveolar concentration (MAC)? The minimum alveolar concentration (MAC) of N_2O is 104%. How does minimum alveolar concentration (MAC) relate to the potency of N_2O?

Minimum alveolar concentration (MAC), is defined as the concentration in the alveoli that will prevent movement in 50% of patients, in response to a painful stimulus like a surgical incision.

Inhalational agents are absorbed in alveoli and the anaesthetic concentration in the brain is directly related to alveolar concentration. Thus, *minimum alveolar concentration (MAC) is inversely related to potency* of the anaesthetic agent.

Nitrous oxide (N_2O) has low blood solubility and small blood gas partition coefficient. So, the transfer of a small amount of anaesthetic from the alveolus to blood capillary raises the partial pressure in the capillary. This accounts for less uptake of anaesthetic from the alveoli into the bloodstream, thus increasing the alveolar partial pressure to 104%. Since the potency of anaesthetic agent is related inversely to MAC and the alveolar partial pressure is high, that is, 104%, the potency of N_2O is poor.

Qd. Sevoflurane is a potent anaesthetic agent despite of its low blood/gas partition coefficient, in contrast to N_2O, a low potent anaesthetic agent having low blood gas partition coefficient. Explain why?

The high potency of sevoflurane despite its low blood/gas partition coefficient is due to its *high oil/gas partition coefficient* and low minimum alveolar concentration (MAC).

In contrast, nitrous oxide (N_2O) has low potency because of its low blood/gas partition coefficient and high minimum alveolar pressure (MAP).

Qe. Why is the induction of anaesthesia caused by N_2O relatively rapid than ether?

Nitrous oxide has low blood/gas partition coefficient, so there is rapid rise in partial pressure in blood capillary which achieves the partial pressure in the CNS quickly and induction time is short.

Conversely, ether is very blood soluble anaesthetic agent, so a much larger amount of anaesthetic must dissolve in the blood to raise the partial pressure in the capillary and hence, a longer period is necessary to achieve the anaesthetic partial pressure in the CNS. Thus, induction with ether is slow and prolonged.

Qf. Why is 100% oxygen inhalation continued for a few minutes after discontinuing N_2O, instead of directly switching over to air?

When anaesthesia is terminated, N_2O having low blood solubility rapidly diffuses from bloodstream into alveoli due to high partial pressure difference between two compartments. This dilutes the alveolar air and partial pressure of O_2 in alveoli is reduced resulting in hypoxia called diffusion hypoxia. Diffusion hypoxia is not of much significance if cardiopulmonary reserve is normal but maybe dangerous if it is low. To counteract this effect, pure oxygen is routinely administered for a few minutes following anaesthesia with nitrous oxide.

Note: This phenomenon is not significant with other anaesthetics because they are administered at low concentration (0.2–0.4%) and cannot dilute alveolar air by more than 1–2% in any case, whereas N_2O is administered at 70–80% concentration displacing up to 1 L/min of air that would otherwise have been inhaled.

Qg. What is the advantage of combining halothane with nitrous oxide?

1. Halothane is not a good analgesic. Its analgesic action is compensated by combining with nitrous oxide which is a strong analgesic.
2. Nitrous oxide has low potency and the anaesthetic action is insufficient if used as a single agent. It is often combined with a more potent inhalational anaesthetic such as halothane to achieve the 'second gas effect'.

Qh. If JK has a history of pre-existing ventricular arrhythmias, should halothane be used as an anaesthetic agent?

Halothane has arrhythmogenic potential and sensitizes the heart to catecholamine-induced ventricular dysrhythmias. Therefore, they are used with caution or avoided in patients with history of pre-existing ventricular arrhythmias.

Qi. Mention the benefits of sevoflurane as an anaesthetic agent.

- Sevoflurane is an ideal induction agent because it has a pleasant smell, rapid onset, and there is lack of airway irritation.
- It has adequate potency, appropriate solubility and is an effective bronchodilator. It is the preferred agent for induction in adult and pediatric patients.
- It has rapid recovery profile and is used for outpatient anaesthesia.
- There is less myocardial depression and arrhythmogenic potential than halothane and there is minimal to no risk of hepatotoxicity.

Qj. How is sevoflurane superior to methoxyflurane, enflurane or isoflurane as an anaesthetic agent?

- Sevoflurane is non-inflammable, volatile halogenated agent which is completely fluorinated analog of isoflurane. The fluorinated agents produce rapid awakening, especially in obese patients following prolonged surgery.
- Isoflurane, enflurane and methoxyflurane containing fluoride that is not completely fluorinated. They are metabolized to fluoride ions to cause polyuric renal failure and hence contraindicated in renal failure.
- Enflurane lowers the seizure threshold and is contraindicated in epilepsy.
- Isoflurane exhibits the phenomenon of 'coronary steal' by causing redistribution of blood from regions of poor perfusion to regions of normal perfusion increasing the chances of myocardial ischaemia particularly in patients with coronary artery disease. Sevoflurane does not produce 'coronary steal' and offers an advantage over isoflurane.

CASE 2: HALOTHANE-INDUCED HEPATOTOXICITY

10 days after the surgery, JK returns to the hospital with complaints of yellowish discolouration of the eye and symptoms of nausea and vomiting. On physical examination, there is tenderness on the right side of the abdomen.

He had undergone appendicectomy under halothane anaesthesia.

Laboratory findings reveal ↑ bilirubin, ↑ serum transaminases, ↑ alkaline phosphatase and ↑ eosinophils.

Biopsy shows massive centrilobular hepatic necrosis.

The clinical condition was diagnosed as type II (fulminant) halothane hepatotoxicity.

Qa. Explain the underlying mechanism for halothane-induced hepatic dysfunction in case of JK.

Halothane undergoes both oxidative and reductive metabolism by hepatic cytochrome P450. Hepatotoxicity can result from these CYP-catalyzed transformations. Halothane oxidation, the major metabolic pathway, leads to the production of the reactive electrophile trifluoroacetylchloride and by subsequent acylation of liver proteins, results in the formation of trifluoroacetylated protein neoantigens. In predisposed individuals, these neoantigens elicit antibody formation, and upon subsequent exposure to halothane, a secondary immune response elicits hepatic necrosis.

CASE 3: HALOTHANE-INDUCED ANAESTHESIA IN PREGNANCY

MT, a 27-year-old pregnant female requires anaesthesia and analgesia in the following situations:

1. **For analgesia during labour**
2. **For external or internal version of fetus during late pregnancy.**

Qa. Comment on the use of halothane, in the above-mentioned clinical situations.

Halothane has moderate relaxation effect on smooth muscles such as bronchi and uterus. Its use during labour can prolong delivery and cause postpartum haemorrhage and thus avoided.

Halothane may be a useful anaesthetic option for conducting procedures such as external or internal version of fetus during late pregnancy.

Halothane should be used during pregnancy only if the possible benefits outweigh the possible risk to the unborn baby.

CASE 4: ETOMIDATE USE FOR ANAESTHESIA

RX with a history of ischaemic heart disease was posted for coronary artery bypass grafting. He is a known case of hypertension and diabetes.

Induction of anaesthesia was done using intravenous injection of etomidate (0.2 mg/kg).

Qa. Explain the advantages and limitations of etomidate over other inducing agents like propofol or thiopentone, used for anaesthesia considering the case of RX.

Etomidate has a rapid onset and brief period of action, thus acting as a suitable inducing agent for anaesthesia. It has a very stable cardiovascular profile and is usually recommended for induction in patients with poor left ventricular reserve.

Propofol similar to etomidate has rapid onset and short duration of action when given intravenously and is used for induction at a dose of 1.5 to 2.5 mg/kg. It usually causes reduction in systemic vascular resistance and arterial pressure by 15 to 40% and can cause direct myocardial depression at doses above 0.75 mg/kg.

Etomidate has gained favour over thiopental on account of the larger margin between the anaesthetic dose and the dose needed to produce cardiovascular depression. It is more rapidly eliminated from the body than thiopental, and thus less likely to cause a prolonged hangover.

Pain and phlebitis are common side effects related to etomidate which can be reduced with prior injection of lidocaine. The risk of nausea or vomiting makes etomidate a less ideal drug for use in an ambulatory setting. Etomidate suppresses the production of adrenal steroids, an effect that has been associated with an increase in mortality in severely ill patients. It should be avoided in patients at risk of having adrenal insufficiency, e.g. in sepsis.

Qb. Given that RX has a medical history of hypertension and coronary artery disease, do you think ketamine should be used as an anaesthetic agent in case of RX?

Ketamine stimulates the cardiovascular system resulting in an increase in heart rate, blood pressure and increase in cardiac output, mediated principally through the sympathetic nervous system. Consequently, there is an increase in myocardial oxygen demand and work load on the heart. It is thus contraindicated in patients with angina, coronary artery disease and hypertension.

CASE 5: KETAMINE USE FOR ANAESTHESIA

LY, a 37-year-old adult female was admitted to the regional burn center for her burn injuries. She received IV ketamine during burn wound care.

Qa. Describe the anaesthetic state produced by ketamine.

Ketamine produces a hypnotic state quite distinct from that of other anaesthetics termed as *'dissociative anaesthesia.'* Ketamine has cataleptic, amnestic, profound analgesic and dose-dependent anaesthetic actions. The cataleptic state is an akinetic state with the loss of orthostatic reflexes, but without impairment of consciousness. The dissociative state produced by ketamine is unique in which the patient appears awake, but is detached from the surroundings with eyes remaining open.

Qb. Mention the rationale for use of ketamine in the management of severe burn dressing.

Ketamine has been widely used to provide *analgesia* in burn dressing changes, during excision and grafting and for *sedation.* Its main action is to produce *dissociative anaesthesia.* By acting at the level of NMDA receptors as a non-competitive NMDA receptor antagonist, ketamine reduces the presynaptic release of glutamate in addition to complex interactions with opioid receptors. Ketamine is thus thought to prevent the induction of central sensitization acting as an antiallodynic and antihyperalgesic agent.

Qc. What is the advantage of ketamine over opioid in the management of burn wound care?

The major advantage of ketamine in burns is that unlike opioids, it usually preserves airway and spontaneous respiratory function in addition to providing good sedation and profound analgesia.

It *preserves cardiovascular stability* in patients at risk for hypotension as in burn patients. Cardiovascular effects are indirect and are due to inhibition of both central and peripheral catecholamine reuptake.

Note: Opioids are known to cause respiratory depression and hypotension.

Qd. What is the effect of ketamine on muscle relaxation? In which surgical procedures is ketamine a suitable anaesthetic drug to be used?

Ketamine causes increased muscle tone, so it is not appropriate for surgical procedures that require muscle relaxation. It is useful for small procedures which require minimal or no muscle relaxation such as head and neck surgery, traumatic wound, severe burn dressing, cardiac catheterization and angiography.

Qe. Mention few contraindications to the use of ketamine. What are the common side effects of ketamine?

Ketamine can cause an increase in blood pressure, intraocular pressure and intracranial pressure or pressure in the brain. Therefore, *ketamine should be avoided in surgeries in patients with brain swelling, glaucoma, brain lesion or tumuor.*

Emergence delirium characterized by hallucinations, vivid dreams and delusions is a frequent complication and leads to serious patient dissatisfaction and can also complicate postoperative management. Other important side effects of ketamine include increased secretions and the risk of laryngospasm.

Qf. Why is ketamine classified as schedule X drug?

Ketamine has potential for abuse and therefore classified as schedule X drug. It can be used as 'date rape drug' when mixed with drinks and is known as 'club drug'.

CASE 6: KETAMINE USE AS AN ANAESTHETIC AGENT IN HEART DISEASE

A one-year-old child KL diagnosed with congenital heart disease with right-to-left shunt undergoes surgery. Ketamine IV was used as an inducing agent for anaesthesia.

Qa. Explain the rationale for using ketamine as an anaesthetic agent in case of KL.

For induction of patients, especially children with congenital heart disease with right-to-left shunt, ketamine is the anaesthetic drug of choice due to its favourable cardiovascular effects. Increased sympathetic flow results in increased systemic vascular resistance and this effect decreases the right-to-left shunt. Ketamine preserves intra and postoperative hemodynamic stability. Furthermore, by increasing pulmonary blood flow, it improves oxygenation.

CASE 7: ANAESTHESIA IN BRONCHIAL ASTHMA

As an anaesthesiologist, you are requested to administer general anaesthesia to a 25-year-old male RJ with a history of bronchial asthma.

Qa. Which anaesthetic drugs would you recommend for RJ?

Propofol and ketamine inhibit bronchoconstriction, decreasing the risk of bronchospasm during anaesthesia induction. Propofol appears to be superior to thiopental and etomidate as an inducing agent for anaesthesia in bronchial asthma.

Halothane, enflurane and isoflurane are potent bronchodilators and can be helpful even in status asthmaticus.

CASE 8: ANAESTHESIA FOR DAY-CARE SURGERIES

A 42-year-old female ST, undergoes an oral surgery procedure. Propofol is used as an outpatient general anaesthetic agent.

Qa. Explain why propofol is preferred in day-care surgical procedures.

Propofol is a phenol agent with *rapid onset and short duration of action* and is used for induction as well as maintenance. It has a short half-life due to very high clearance. This contributes to rapid recovery from anaesthetic effect with minimal residual sedation. Additionally, it has *antiemetic properties* making it popular for outpatient procedures.

Qb. What is the likely cause of propofol infusion syndrome (PRIS)? Describe the clinical features of propofol infusion syndrome.

There is an association between propofol infusion syndrome (PRIS) and propofol infusions at doses higher than 4 mg/kg/h for greater than 48 h duration. Propofol can cause abnormalities consistent with the *disruption of fatty acid oxidation*, causing peripheral and cardiac muscle cell damage. The muscle cell damage is created by *impaired entry of long chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain.*

The clinical features of propofol infusion syndrome are acute refractory bradycardia leading to asystole, metabolic acidosis, rhabdomyolysis, hyperlipidaemia and enlarged or fatty liver.

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Chapter

31

Skeletal Muscle Relaxants

CASE 1: CONSIDERATIONS FOR APPROPRIATE USE OF MUSCLE RELAXANTS

A 45-year-old male HN, underwent major abdominal surgery under general anaesthesia. Premedication with diazepam 10 mg and atropine 0.6 mg is followed by induction of anaesthesia with thiopentone 400 mg. The trachea was then intubated following succinylcholine 75 mg, intermittent positive pressure ventilation (IPPV) was started with 1% halothane carried in a mixture of 5 litres of nitrous oxide and 3 litres of oxygen. Muscle tone returned and pancuronium 6 mg was given with pentazocine 15 mg.

Qa. How do you classify skeletal muscle relaxants?

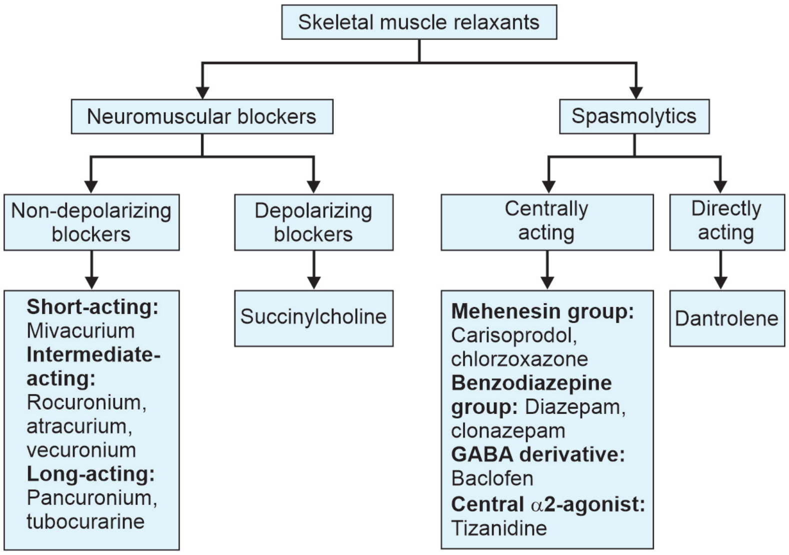

Skeletal muscle relaxants
Neuromuscular blockers
Spasmolytics
Non-depolarizing blockers
Depolarizing blockers
Centrally acting
Directly acting
Short-acting: Mivacurium
Intermediate-acting: Rocuronium, atracurium, vecuronium
Long-acting: Pancuronium, tubocurarine
Succinylcholine
Mehenesin group: Carisoprodol, chlorzoxazone
Benzodiazepine group: Diazepam, clonazepam
GABA derivative: Baclofen
Central α2-agonist: Tizanidine
Dantrolene

Fig. 31.1: Classification of skeletal muscle relaxants

Drugs which relax skeletal muscles fall into two major groups:

1. **Neuromuscular blocking drugs** interfere with transmission at the neuromuscular end-plate and lack central nervous system activity. These compounds are used primarily as adjuncts to general anaesthesia during surgical procedures and in intensive care units to cause paralysis.

2. Spasmolytic group includes 'centrally-acting' and 'directly-acting' muscle relaxant drugs.

Centrally-acting muscle relaxants act at multiple sites in the central nervous system (CNS) rather than at the neuromuscular end-plate. Examples of centrally-acting muscle relaxant drugs are carisoprodol, chlorzoxazone, diazepam, clonazepam, baclofen, and tizanidine.

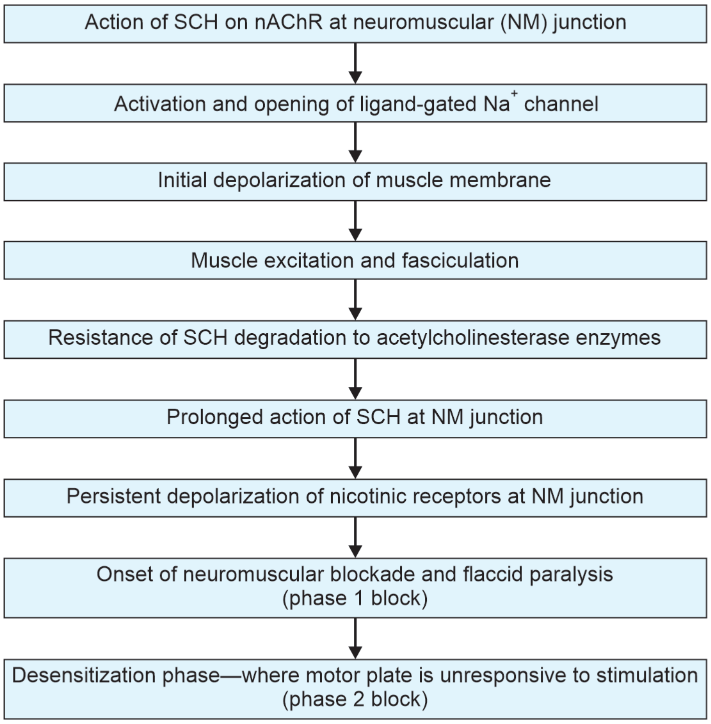
Directly-acting muscle relaxants act in or near skeletal muscle with no significant central effects. Directly-acting drugs are dantrolene and botulinum toxin.

Qb. What is the rationale for the use of succinylcholine in tracheal intubation procedure?

Succinylcholine (SCH) is one of the most commonly used neuromuscular blocking agent for rapid sequence induction because it has a rapid onset of effect, short duration of action and produces profound depth of neuromuscular blockade. Injected intravenously at a dose of 1 mg/kg, its use can expedite rapid endotracheal intubation, facilitate surgical procedures, and aid in mechanical ventilation by relaxation of skeletal muscles.

Typically, after administering succinylcholine for intubation, a non-depolarizing neuromuscular blocker is given to maintain neuromuscular blockade. Succinylcholine given first may enhance the depth of block induced by a subsequent dose of non-depolarizing neuromuscular blocker.

Qc. How does succinylcholine act as a neuromuscular blocking agent in facilitating tracheal intubation?


Action of SCH on nAChR at neuromuscular (NM) junction
Activation and opening of ligand-gated Na$^+$ channel
Initial depolarization of muscle membrane
Muscle excitation and fasciculation
Resistance of SCH degradation to acetylcholinesterase enzymes
Prolonged action of SCH at NM junction
Persistent depolarization of nicotinic receptors at NM junction
Onset of neuromuscular blockade and flaccid paralysis (phase 1 block)
Desensitization phase—where motor plate is unresponsive to stimulation (phase 2 block)

SCH: Succinylcholine; nAChR: Nicotinic acetylcholine receptor

Fig. 31.2: Succinylcholine action as a neuromuscular blocking agent

Succinylcholine (SCH) binds to nicotinic acetylcholine receptors (nAChR), opening Na$^+$ channels, causing initial depolarization of cell membrane at motor end-plate leading to skeletal muscle excitation and muscle fasciculations. Persistent action of succinylcholine at the neuromuscular junction causes prolonged depolarization, followed by block of neuromuscular transmission and flaccid paralysis *(phase 1 block)*.

This is followed by *desensitization phase* when the sodium channels are closed and the muscle membrane gradually repolarizes. During this phase the motor end-plate is unresponsive to further incoming depolarizing signals and flaccid paralysis continues till the muscle membrane is completely repolarized *(phase 2 block)*.

Qd. Although both acetylcholine and succinylcholine act through similar mechanisms, explain why acetylcholine is not used as a neuromuscular blocker.

Acetylcholine and succinylcholine, both act through a similar mechanism producing depolarisation and muscle contraction. However, acetylcholine does not produce neuromuscular blockade, because it has a very short duration of action (few milliseconds) due to rapid hydrolysis by acetylcholinesterases to acetic acid and choline. But succinylcholine is resistant to and is not metabolized by acetylcholinesterases leading to persistent depolarization of the muscle fibres, thus resulting in well-recognized muscle fasciculations and paralysis of the patient.

Qe. What is the pharmacological basis of use of pancuronium during abdominal surgery in case of HN?

Pancuronium is a non-depolarizing neuromuscular blocker with a rapid onset of effect and a long duration of action. It is useful for maintaining muscle relaxation during abdominal surgery.

Pancuronium competes with acetylcholine for the nicotinic receptors at the neuromuscular junction of skeletal muscles, thereby inhibiting the action of acetylcholine and blocking the neural transmission without depolarizing the postsynaptic membrane. This may lead to skeletal muscle relaxation and paralysis.

Qf. How does organ dysfunction and advanced age influence the actions of pancuronium? How is atracurium better than pancuronium in this regard?

- Pancuronium is eliminated primarily by the kidney and hence the clearance of pancuronium is decreased and elimination half-life is prolonged in patients with renal failure.
- Patients with liver disease due to either cholestasis or cirrhosis show increased volume of distribution which might be responsible for the relative resistance of these patients to pancuronium-induced block.
- Clearance is decreased and duration of action of pancuronium is prolonged in patients of advanced age.

Atracurium and its isomer *cis*-atracurium are independent of both hepatic and renal function because they are eliminated via Hoffmann degradation. *Cis*-atracurium has a favourable side effect profile compared to atracurium because of lack of histamine releasing property. The majority of adverse reactions associated with atracurium administration are related to histamine release. Common side effects are flushing and erythema. Less commonly, more severe adverse effects include bradycardia, bronchospasm, dyspnea, hypotension, laryngospasm, tachycardia, urticaria and wheezing. Both compounds can be administered as intermittent boluses or as a continuous infusion.

Case Ccontinued

After pancuronium has been used for intra-abdominal surgery of long duration and the neuromuscular blockade has been reversed by neostigmine, the surgeon announces that another 15 minutes are needed to retrieve a missing sponge.

Qa. At this point, if succinylcholine is used to re-establish neuromuscular blockade, what will be the effect of prior administration of neostigmine on neuromuscular blockade action of succinylcholine? Explain.

When succinylcholine is given soon after the administration of neostigmine, the duration of muscle relaxation is prolonged. Prolonged muscle relaxation may be attributed to the inhibitory action of neostigmine on acetylcholinesterases, thus increasing the concentration of acetylcholine at the neuromuscular junction, resulting in potentiation of succinylcholine-induced neuromuscular blockade. Thus, phase I blockade of succinylcholine is potentiated by the effects of cholinesterase inhibitors.

Qb. Explain the rationale for the use of neostigmine for reversing neuromuscular blockade caused by pancuronium after the completion of surgery under general anaesthesia.

Non-depolarizing neuromuscular blocking agents such as pancuronium act by competing with acetylcholine, for binding to postsynaptic nicotinic receptor sites in the skeletal muscle neuromuscular junction. Because the interaction of non-depolarizing neuromuscular blockers with acetylcholine receptor binding sites is competitive, neuromuscular blockade can be overcome by increasing the concentration of acetylcholine. Thus, neostigmine is useful in reversing neuromuscular blockade by increasing the concentration of acetylcholine through acetylcholinesterase inhibition.

CASE 2: SUCCINYLCHOLINE: ADVERSE EFFECTS AND PRECAUTIONS

In case of HN, consider a situation where, after 45 minutes of surgical procedure, the medical team is unable to extubate the patient due to prolonged muscle paralysis suspected to be induced by succinylcholine. The patient is then transferred to the intensive care unit for the management of succinylcholine-induced muscle paralysis and apnoea.

Qa. What are the likely reasons for succinylcholine-induced apnoea?

There are two types of plasma cholinesterase enzymes. True cholinesterase or acetylcholinesterase and atypical plasma cholinesterases (pseudocholinesterase or butyrylcholinesterase). Succinylcholine is hydrolysed and broken down by atypical plasma cholinesterase enzyme, butyrylcholinesterase, synthesized by the liver. The neuromuscular block induced by succinylcholine is *prolonged* by a *decreased concentration* or *activity of the enzyme*.

Quantitative deficiencies of pseudocholinesterase may be observed in liver disease, advanced age, malnutrition, pregnancy, malignancies, collagen vascular disease and hypothyroidism; they slightly prolong the duration of blockade with succinylcholine.

There may also be qualitative deficiencies in pseudocholinesterase (i.e. the activity of the enzyme is impaired). These are genetic diseases and as such can be present in heterozygotic or homozygotic forms.

Qb. What is the relationship between succinylcholine-induced apnoea and dibucaine number in patients with genetic deficiency of plasma cholinesterases?

Succinylcholine-induced neuromuscular blockade can be significantly prolonged if the patient has an abnormal genetic variant of butyrylcholinesterase. The variant was found to respond to dibucaine differently than normal butyrylcholinesterase does. Dibucaine when administered into the plasma, inhibits normal plasma cholinesterase by 80%, whereas the atypical plasma cholinesterase is inhibited by only 20%.

Patient type	*Dibucaine number*	*Interpretation*
Patient with normal pseudocholinesterase	80	Normal individual
Patient is heterozygous for atypical pseudocholinesterase	40 to 60	Patient will have a moderately prolonged and usually clinically insignificant block with SCH
Patient is homozygous for atypical pseudocholinesterase	20	Patient will have an extremely prolonged block with SCH

Qc. In case of recent, severe tissue injury or burns, should succinylcholine be used as a muscle relaxant? Explain with reasons.

Patients with recent burns or acute trauma are susceptible to have *hyperkalemic rhabdomyolysis*, which is exacerbated by the administration of succinylcholine chloride and can result in ventricular dysrhythmias or even death. Therefore, administration of succinylcholine is contraindicated in these patients.

In the normal innervated mature muscle, the acetylcholine receptors (AChRs) are located in the junctional area. In certain pathologic states such as direct muscle trauma and/or burn injury, *there is upregulation (increase) of AChRs* spreading throughout the muscle membrane, with the *additional expression of two new isoforms of AChRs*. The depolarisation of these AChRs that are spread throughout the muscle membrane by succinylcholine and its metabolites leads to *potassium efflux from the muscle leading to hyperkalemia.*

Qd. It was observed that the intraocular pressure (IOP) after succinylcholine injection increased within 1 minute, obtained peaks at 2 to 4 minutes, and subsided by 6 minutes. Mention the likely reason for the rise in IOP.

The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils or transient dilatation of choroidal blood vessels or both thus decreasing the intraocular pressure (IOP).

CASE 3: TUBOCURARINE-INDUCED HYPOTENSION

A 47-year-old male JK, was scheduled for gastric surgery. He had a history of asthma but was completely free of symptoms and signs at the time of operation. Initially, succinylcholine was used to induce muscle relaxation to facilitate tracheal intubation. To maintain muscle relaxation, d-tubocurarine was administered, following which JK developed severe bronchospasm and hypotension with d-tubocurarine.

Qa. Explain the underlying reason for severe bronchospasm and hypotension in JK. How could this have been avoided in case of JK?

The severe bronchospasm and hypotension experienced by JK could be possibly due to D-tubocurarine causing marked histamine release by a direct effect on mast cells causing hypotension, bronchospasm and salivary secretions. At higher doses, it can produce ganglionic blockade contributing to hypotension.

Newer non-depolarizing relaxants such as pancuronium, vecuronium, rocuronium have fewer side effects and superior pharmacokinetic profiles. They release histamine and produce ganglionic blockade to a much lesser extent compared to d-tubocurarine, the prototype non-depolarizing skeletal muscle relaxant. D-tubocurarine is rarely used nowadays. Hence, the adverse effects could have been avoided by using newer non-depolarizing relaxants.

CASE 4: MALIGNANT HYPERTHERMIA CAUSED BY DRUG INTERACTION

A 45-year-old female patient RY, operated for parotid tumour presented with features of suspected malignant hyperthermia. Anaesthesia was induced on propofol and succinylcholine and ventilated with oxygen and halothane. Following succinylcholine administration, laryngoscopy was difficult to perform because of masseter rigidity. There was a rise in HR and BP to 150 beats/min and 180 mmHg, respectively. There was associated rise in temperature with maximum reading of 104 degree F recorded by nasopharyngeal probe. Serum potassium concentration was elevated.

Qa. Identify the possible drug interaction in case of RY.

Malignant hyperthermia is triggered in susceptible individuals primarily by volatile inhalational anaesthetic agents and the muscle relaxants such as succinylcholine. In case of RY, co-administration of succinylcholine with halothane could have possibly triggered malignant hyperthermia.

Qb. What is the underlying mechanism for malignant hyperthermia? How would you explain the signs and symptoms presented by RY? Which drug is used for the immediate treatment of malignant hyperthermia?

In malignant hyperthermia, the ryanodine receptor of sarcoplasmic reticulum of skeletal muscle that controls calcium release is abnormal. This causes uncontrolled release of calcium and its accumulation in the skeletal muscle causing muscle fibres to contract, resulting in a massive metabolic reaction.

The increased aerobic and glycolytic metabolism causes increased heat production, activation of the sympathetic nervous system, hyperkalemia, disseminated intravascular coagulation (DIC), multiple organ dysfunction and failure. Early clinical signs of malignant hyperthermia include an increase in end-tidal carbon dioxide, tachycardia, muscle rigidity, tachypnea and hyperkalemia. Later signs include fever, myoglobinuria, and multiple organ failure.

Dantrolene, a directly-acting muscle relaxant, is used to treat the reaction by stopping the release of calcium into the muscle. Other medications may be given to correct the body's metabolic imbalance and treat complications.

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Case-Based Learning in PHARMACOLOGY *for* Undergraduate Medical Students

The latest Competency Based Medical Education Guidelines for the undergraduate students lay emphasis on 'Outcome Based Learning'. Problem based learning and Integrated teaching are innovative teaching-learning methods to enhance learning outcomes. There is scarcity of books to cater to the needs of the students and teachers. This book aims to bridge the gap between theoretical knowledge and clinical practice. Clinically relevant topics are selected and hypothetical case scenarios are designed based on learning objectives. Each case is followed by a series of questions with appropriate answers. The case presentation with question-answer format covers major pharmacological principles of the topic.

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- It includes a broader coverage of topics of pharmacology having clinical relevance, and each topic has been dealt in-depth to strengthen the concepts and makes learning more effective.
- Hypothetical case scenarios are designed and the principles of pharmacology in drug use is discussed in a question-answer format progressing stepwise from the basics to higher learning levels of each topic. The book will be beneficial for different categories of learners—poor, medium and advanced.
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- List of resources (i.e. references, books) for further reading has been given at the end of each chapter. This will provide authenticity to the content and instill confidence in the minds of the readers.
- Structure and content of this book is unique and makes learning effective and interesting.

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